



**PasTest<sup>®</sup>**  
Dedicated to your success

# Essential Revision Notes in Paediatrics for the MRCPCH



## Third Edition

Mark Beattie  
Mike Champion

# **Essential Revision Notes in Paediatrics for the MRCPCH**

## **Third edition**

Edited by

**Dr R M Beattie BSc MBBS MRCP FRCPCH**  
Consultant Paediatric Gastroenterologist  
Paediatric Medical Unit  
Southampton General Hospital  
Southampton

**Dr Mike Champion BSc MBBS MRCP FRCPCH**  
Consultant in Paediatric Inherited Metabolic Disease  
Evelina Children's Hospital  
Guy's and St Thomas' NHS Foundation Trust  
London



# **PasTest**

Dedicated to your success

**Essential Revision Notes in  
Paediatrics for the MRCPCH  
Third edition**



**PasTest**

Dedicated to your success

© 2012 PATEST LTD  
Egerton Court  
Parkgate Estate  
Knutsford  
Cheshire  
WA16 8DX  
Telephone: 01565 752000

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior permission of the copyright owner.

Third edition 2012  
Second edition 2006  
First published 2002

ISBN 978 1905635 764  
eISBN 978 1909491 045

A catalogue record for this book is available from the British Library.

The information contained within this book was obtained by the author from reliable sources. However, while every effort has been made to ensure its accuracy, no responsibility for loss, damage or injury occasioned to any person acting or refraining from action as a result of information contained herein can be accepted by the publishers or author.

**PasTest Revision Books and Intensive Courses**

PasTest has been established in the field of undergraduate and postgraduate medical education since 1972, providing revision books and intensive study courses for doctors preparing for their professional examinations.

**Books, courses and online revision available for:**

Medical undergraduates, MRCP, MRCP Parts 1 and 2, MRCPCH Parts 1 and 2, MRCS, MRCOG, DRCOG, DCH, FRCA, Dentistry.

**For further details contact:**

**PasTest, Freepost, Knutsford, Cheshire WA16 7BR**

**Tel: 01565 752000      Fax: 01565 650264**  
**[www.pastest.co.uk](http://www.pastest.co.uk)      [enquiries@pastest.co.uk](mailto:enquiries@pastest.co.uk)**

Text prepared in the UK by Keytec Typesetting Ltd, Bridport, Dorset  
Printed and bound in the UK by Page Bros (Norwich) Ltd



## [Contributors](#)

## [Preface to the Third edition](#)

## CHAPTERS

### [1. Cardiology](#)

Robert Tulloh

### [2. Child Development, Child Mental Health and Community Paediatrics](#)

Joanne Philpot and Ruth Charlton

### [3. Child Protection and Safeguarding](#)

Joanne Philpot and Ruth Charlton

### [4. Clinical Governance](#)

Robert Wheeler

### [5. Clinical Pharmacology and Toxicology](#)

Steven Tomlin

### [6. Dermatology](#)

Helen M Goodyear

### [7. Emergency Paediatrics](#)

Serena Cottrell

### [8. Endocrinology and Diabetes](#)

Heather Mitchell and Vasanta Nanduri

### [9. Ethics and Law](#)

Vic Larcher and Robert Wheeler

### [10. Gastroenterology and Nutrition](#)

Mark Beattie and Hemant Bhavsar

### [11. Genetics](#)

Natalie Canham

### [12. Haematology and Oncology](#)

Michael Capra

### [13. Hepatology](#)

Nancy Tan and Anil Dhawan

#### **14. Immunology**

Pamela Lee and Bobby Gaspar

#### **15. Infectious Diseases**

Nigel Klein and Karyn Moshal

#### **16. Metabolic Medicine**

Mike Champion

#### **17. Neonatology**

Grenville F Fox

#### **18. Nephrology**

Christopher J D Reid

#### **19. Neurology**

Neil H Thomas

#### **20. Ophthalmology**

Ken K Nischal

#### **21. Orthopaedics**

Vel K Sakthivel

#### **22. Respiratory**

Rebecca Thursfield and Jane C Davies

#### **23. Rheumatology**

Nathan Hasson

#### **24. Statistics**

Angie Wade

#### **25. Surgery**

Merrill McHoney

#### **Picture Permissions**

#### **Index**

## Contributors to the Third Edition

---

**Dr R M Beattie BSc MBBS MRCP FRCPCH**

Consultant Paediatric Gastroenterologist, Southampton General Hospital, Southampton

**Hemant S Bhavsar MBBS DCH MRCPCH MD**

Specialist Registrar in Paediatric Gastroenterology, Birmingham Children's Hospital, Birmingham

**Natalie L E Canham MBChB BA (Hons) MRCP (Paeds)**

Consultant in Clinical Genetics, North West Thames Regional Genetics Service, Northwick Park Hospital, Harrow, Middlesex

**Michael L Capra MBBCH DCH Dip. Obst FRPCH MMedSci (Clinical Education)**

Consultant Paediatric Oncologist, Department of Haematology/Oncology, Our Lady's Children's Hospital, Crumlin, Dublin 12

**Michael P Champion BSc MBBS MRCP FRCPCH**

Consultant in Paediatric Inherited Metabolic Disease, Evelina Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust, London

**Ruth Charlton MBBS MRCP MRCPCH**

Consultant Paediatrician, Epsom and St. Helier University Hospitals NHS Trust, Epsom, Surrey

**Serena Cottrell BSc (Hons) MBBS MRCPI MMed Sci FRCPCH**

Lead Consultant in Paediatric Emergency Medicine, Queen Alexandra Hospital, Portsmouth

**Jane C Davies MBChB MRCP MRCPCH MD**

Honorary Consultant, Paediatric Respiratory Department, Royal Brompton Hospital, London

**Professor Anil Dhawan MD FRCPCH**

Paediatric Liver Centre, Kings College Hospital NHS Foundation Trust, London

**Grenville F Fox MBChB MRCP FRCPCH**

Consultant Neonatologist, Evelina Children's Hospital Neonatal Unit, Guys and St Thomas' Hospital

Foundation Trust, London

**Professor Bobby Gaspar BSc MBBS MRCP (UK) PhD MRCPCH**

Professor of Paediatrics and Immunology, Centre for Immunodeficiency, Molecular Immunology Unit, UCL Institute of Child Health, University College London, London

**Helen M Goodyear MBChB MRCP FRCPCH MD MMed**

Consultant Paediatrician and Associate Postgraduate Dean, Birmingham Heartlands and Solihull NHS Trust, Department of Child Health, Birmingham

**Nathan Hasson MBChB FRCPCH**

Consultant Paediatric Rheumatologist, The Portland Hospital, London

**Professor Nigel Klein BSc MBBS MRCP FRCPCH PhD**

Professor of Infection and Immunology, University College London, Consultant in Infectious Diseases, Great Ormond Street Hospital, London

**Vic Larcher BA MA MB BChir MRCP FRCPCH**

Consultant in Adolescent Medicine (Chronic Fatigue) and in Clinical Ethics, Adolescent Medicine Department, Level 10 Southwood Building, Great Ormond Street Hospital, London

**Pamela Lee MBBS MRCPCH**

Honorary Clinical Fellow, Great Ormond Street Hospital NHS Trust, London

**Merrill McHoney FRCS(Paed Surg) PhD**

Consultant Paediatric Surgeon, Royal Hospital for Sick Children Edinburgh, Edinburgh

**Heather Mitchell BM.BCh MD MA FRCPCH MRCP(Paeds) MRCGP DCH DRCOG**

Consultant Paediatrician, West Hertfordshire Hospitals Trusts

**Karyn Moshal MBChB MRCP (UK) MRCPCH DTM+H**

Consultant in Paediatric Infectious Diseases, Great Ormond Street Hospital for Children, London

**Vasanta R Nanduri MBBS DCH MRCP MD FRCPCH**

Consultant Paediatrician, Watford General Hospital, Watford

**Ken K Nischal FRCOphth**

Director and Professor, UPMC Children's Hospital of Pittsburgh, USA  
Honorary Consultant, Great Ormond Street Hospital for Children, London

**Joanne Philpot BA MBBS MD DCH MRCPCH**

Consultant Paediatrician, Wexham Park Hospital, Slough

**Christopher J D Reid MB ChB MRCP (UK) FRCPCH**  
Consultant Paediatric Nephrologist, Evelina Children's Hospital, London

**Vel K Sakthivel FRCS(Ed), FRCS (Orth)**  
Consultant in Trauma and Orthopaedics, University Hospitals Southampton, Southampton

**Nancy Tan MBBS MMED (Paeds) MRCPCH (Edin) Dip (FP) Derm (S'pore)**  
Consultant, Department of Paediatrics Medicine, KK Women's and Children's Hospital, Singapore

**Neil H Thomas MA MB MChir FRCP FRCPCH DCH**  
Consultant Paediatric Neurologist, Southampton General Hospital, Southampton

**Rebecca Thursfield MBChB MRCPCH**  
Clinical Research Fellow, Dept Paediatric Respiratory Medicine, Royal Brompton Hospital, London

**Stephen R Tomlin FRPharmS ACPP**  
Consultant Pharmacist – Children's Services, Evelina Children's Hospital, London  
Honorary Senior Lecturer, Centre for Paediatric Pharmacy Research, University College School of Pharmacy

**Robert M R Tulloh MA DM FRCP FRCPCH**  
Consultant in Paediatric Cardiology with an interest in Pulmonary Hypertension, Bristol Congenital Heart Centre, Hon reader in Clinical Sciences, University of Bristol  
Director of Medical Education, University Hospitals Bristol NHS Foundation Trust, Bristol

**Angie M Wade MSc PhD CSTAT ILTM**  
Senior Lecturer in Medical statistics, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London

**Robert Wheeler FRCS MS LLB(Hons) LLM**  
Consultant Neonatal and Paediatric Surgeon, Senior Lecturer in Clinical Law, Wessex Regional Paediatric Surgical Centre, Southampton General Hospital, Southampton



## Preface to the Third Edition

---

The first edition of *Essential Revision Notes for the MRCPCH* was in response to the candidates often expressed desire for a single text covering essential information required for the examination in a clear and concise way. The format of the examination has changed considerably over the 10 years since, although the need for a sound knowledge base of the principles and practice of paediatrics remains crucial for success. We have been delighted with the response to the first and second edition of this text and the consistent positive feedback from trainees. The third edition has been completely revised and extensively updated and we hope will continue to be considered as relevant to the examination and future paediatric practice.

We are indebted to the many contributing authors, experts in their fields and expert clinical teachers. We are indebted to PASTEST for their continued enthusiastic support.

We are also indebted to the candidates for their enthusiasm and commitment to the speciality and hope very much that this new edition of *Essential Revision Notes for the MRCPCH* will continue to help trainees to get through their paediatric membership and be useful to them subsequently as an up to date and relevant paediatric textbook.

**Mark Beattie**  
**Mike Champion**

## **CONTENTS**

### **1. Diagnosis of congenital heart disease**

- [1.1 Fetal cardiology](#)
- [1.2 Epidemiology](#)
- [1.3 Cardiac anatomy](#)
- [1.4 Nomenclature for sequential segmental arrangement](#)
- [1.5 Examination technique](#)
- [1.6 Innocent murmurs](#)

### **2. Basic cardiac physiology**

- [2.1 Physiology of adaptation to extrauterine life](#)
- [2.2 Physiology of congenital heart disease](#)
- [2.3 Physiology of heart muscle and heart rate](#)

### **3. Left-to-right shunt**

- [3.1 Atrial septal defect \(ASD\)](#)
- [3.2 Ventricular septal defect \(VSD\)](#)
- [3.3 Persistent ductus arteriosus \(PDA\)](#)
- [3.4 Aortopulmonary window](#)
- [3.5 Others](#)

### **4. Right-to-left shunt**

- [4.1 Tetralogy of Fallot](#)
- [4.2 Transposition of the great arteries](#)
- [4.3 Pulmonary atresia](#)
- [4.4 Ebstein anomaly](#)
- [4.5 Eisenmenger syndrome](#)

## **5. Mixed shunt**

[5.1 Complete atrioventricular septal defects](#)

[5.2 Tricuspid atresia](#)

[5.3 Others](#)

## **6. Obstruction in the well child**

[6.1 Aortic stenosis](#)

[6.2 Pulmonary stenosis](#)

[6.3 Adult-type coarctation of the aorta](#)

[6.4 Vascular rings and slings](#)

## **7. Obstruction in the sick newborn**

[7.1 Coarctation of the aorta](#)

[7.2 Hypoplastic left heart syndrome](#)

[7.3 Critical aortic stenosis](#)

[7.4 Interruption of the aortic arch](#)

[7.5 Total anomalous pulmonary venous connection](#)

## **8. Non-bypass surgery for congenital heart disease**

[8.1 Shunt operation](#)

[8.2 Coarctation of the aorta repair](#)

[8.3 Pulmonary artery band](#)

[8.4 Arterial duct ligation](#)

## **9. Bypass surgery for congenital heart disease**

[9.1 Switch operation](#)

[9.2 Fontan](#)

[9.3 Norwood](#)

[9.4 Rastelli](#)

[9.5 Other operations](#)

## **10. Syndromes in congenital heart disease**

[10.1 Isomerism](#)

[10.2 Trisomy](#)

[10.3 Williams syndrome](#)

[10.4 Noonan syndrome](#)

[10.5 DiGeorge syndrome](#)

[10.6 Alagille syndrome](#)

[10.7 Turner syndrome](#)

[10.8 Marfan syndrome](#)

[10.9 VACTERL](#)

[10.10 Holt–Oram/Thrombocytopenia and absent radius \(TAR\)/Fanconi syndromes](#)

[10.11 CHARGE](#)

[10.12 Pentalogy of Cantrell](#)

[10.13 Dextrocardia](#)

[10.14 Other syndromes](#)

## **[11. Syncope in childhood](#)**

## **[12. Pulmonary hypertension](#)**

[12.1 Persistent pulmonary hypertension of the newborn](#)

[12.2 Increased pulmonary blood flow](#)

[12.3 Chronic hypoxia](#)

[12.4 Pulmonary venous hypertension](#)

## **[13. Drug therapy for congenital heart disease](#)**

[13.1 Heart failure](#)

[13.2 Anticoagulation](#)

[13.3 Pulmonary hypertension](#)

[13.4 Antiarrhythmia](#)

## **[14. Acquired heart disease](#)**

[14.1 Kawasaki disease](#)

[14.2 Dilated cardiomyopathy](#)

[14.3 Hypertrophic cardiomyopathy](#)

[14.4 Suspected bacterial endocarditis](#)

[14.5 Rheumatic fever](#)

[14.6 Pericarditis](#)

## **[15. ECG](#)**

[15.1 The ECG and how to read it](#)

[15.2 Tachycardias](#)

[15.3 Bradycardias](#)

## **[16. Chest X-rays](#)**

[16.1 Cardiac outlines](#)

## **[17. Cardiac catheterization](#)**

[17.1 Diagnostic cardiac catheterization](#)

[17.2 Interventional cardiac catheterization](#)

## **[18. Imaging](#)**

[18.1 Echocardiography](#)

[18.2 Magnetic resonance imaging](#)

[18.3 Positron emission tomography](#)

[18.4 Radionuclear angiography](#)

## 19. Further reading



---

# Cardiology

---

## 1. DIAGNOSIS OF CONGENITAL HEART DISEASE

### 1.1 Fetal cardiology

#### Diagnosis

In the UK, most children (>70%) who require infant surgery for congenital heart disease (CHD) are diagnosed during pregnancy at 16–20 weeks' gestation. This gives a significant advantage to the parents who are counselled by specialists who can give a realistic guide to the prognosis and treatment options. A few undergo termination of pregnancy (depending on the diagnosis). Most continue with the pregnancy and can be offered delivery within the cardiac centre if there could be neonatal complications or if treatment is likely to be needed within the first 2 days of life. Surgical intervention during fetal life is not yet routinely available.

#### Screening (by a fetal cardiologist) is offered to those with:

- Abnormal four-chamber view on routine-booking, antenatal-anomaly ultrasound scan
- Increased nuchal translucency (thickness at back of the neck), which also increases the risk of Down syndrome
- Previous child with or other family history of CHD
- Maternal risk factors, such as phenylketonuria or diabetes
- Suspected Down, or other, syndrome

#### Important normal findings on fetal echocardiography include echodensities:

- Used to be called 'golf balls'
- Found on anterior mitral valve papillary muscle
- Thought to be calcification during development
- No importance for CHD
- Positive association with Down syndrome
- Do not need echocardiogram after delivery

#### Arrhythmias

- Diagnosed at any time during pregnancy: an echocardiogram is required to confirm normal anatomy and to confirm type of arrhythmia. Fetal electrocardiogram (ECG) is not yet a routine investigation
- Multiple atrial ectopics are usually not treated
- Supraventricular tachycardia is usually treated with maternal digoxin or flecainide
- Heart block may be treated with maternal isoprenaline or salbutamol
- Presence of hydrops is a poor prognostic sign

## 1.2 Epidemiology of congenital heart disease

Eight per 1000 live births have CHD, of which the most common are:

• Ventricular septal defect	30%
• Persistent arterial duct	12%
• Atrial septal defect	7%
• Pulmonary stenosis	7%
• Aortic stenosis	5%
• Coarctation of the aorta	5%
• Tetralogy of Fallot	5%
• Transposition of the great arteries	5%
• Atrioventricular septal defect	2%

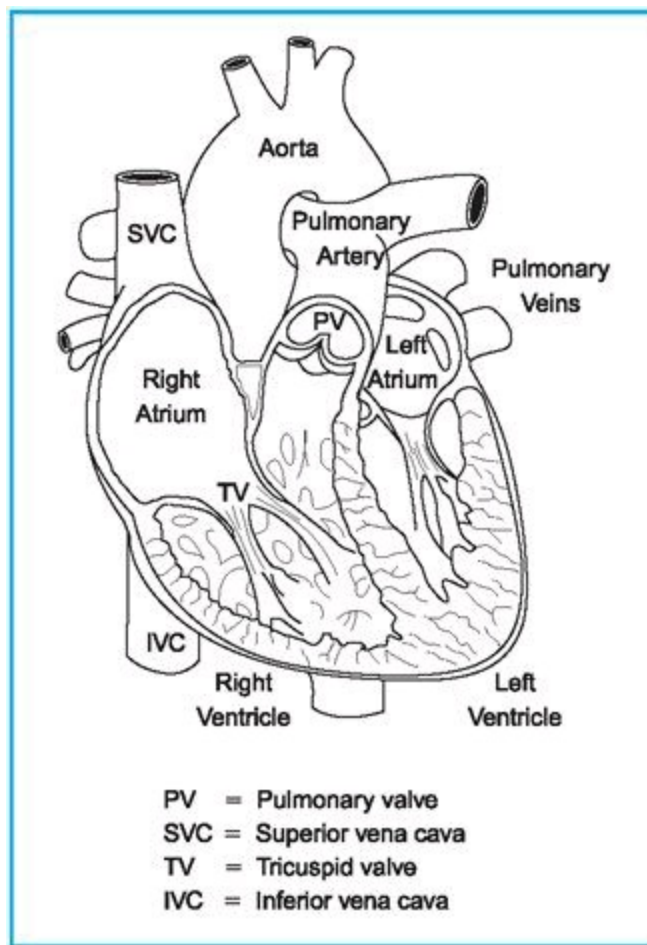
Incidence is increased by a positive family history, so the proportion of live births with CHD will be:

• Previous sibling with CHD	2%
• Two siblings with CHD	4%
• Father with CHD	3%
• Mother with CHD	6%

Incidence also increased by:

- Presence of other anomaly or syndrome
- Parents with an abnormal genotype
- Maternal ingestion of lithium (Ebstein anomaly)
- Third-trimester enterovirus or Cocksackievirus infection (myocarditis, dilated cardiomyopathy)
- Maternal systemic lupus erythematosus (anti-ro, anti-la antibodies leading to congenital heart block)

## 1.3 Cardiac anatomy



Normal heart

## 1.4 Nomenclature for sequential segmental arrangement

The European (as opposed to American) system for complete heart diagnosis is referred to as 'sequential segmental arrangement'. The advantage is that it is no longer necessary to remember the pattern of an eponymous syndrome. The disadvantage is that it is quite long-winded. The idea is that each component is described in turn:

### **Atrial arrangement (atrial situs)**

- Usual (solitus)
- Mirror image (inversus)
- Right isomerism (asplenia syndrome)
- Left isomerism (polysplenia syndrome)

### **Atrioventricular (AV) connection**

#### **Type of atrioventricular connection**

- Biventricular:
  - Concordant
  - Discordant

- Ambiguous (with atrial isomerism)
- Univentricular:
  - Absent left AV connection
  - Absent right AV connection
  - Double inlet AV connection

## **Mode of atrioventricular connection**

- Two AV valves
- Common AV valve
- Straddling right or left AV valve
- Imperforate right or left AV valve
- Overriding right or left AV valve

## **Ventricular topology**

- Right-hand (normal) or left-hand topology

## **Ventriculoarterial connection**

### **Type of ventriculoarterial connection**

- Concordant
- Discordant
- Double outlet
- Single outlet:
  - Common arterial trunk
  - Solitary arterial trunk
  - With pulmonary atresia
  - With aortic atresia

## **Mode of ventriculoarterial connection**

- Two perforate valves
- Left or right imperforate valve

## **Infundibular morphology**

## **Arterial relationships**

## **Associated malformations**

- Position of heart in the chest – left, right or middle
- Systemic and pulmonary veins

- Atrial septum
- Atrioventricular valves
- Ventricular septum
- Semilunar valves
- Anomalies of great arteries (e.g. double aortic arch)

## **Surgical or interventional procedures**

## **Acquired or iatrogenic lesions**

### **1.5 Examination technique**

To many candidates the diagnosis of congenital heart disease is daunting. Certainly, if the candidate examines the child, listens to the heart and then tries to make a diagnosis, this will prove difficult. The following system should be used instead.

## **History**

The history taking is short and to the point. The candidate needs to know:

- Was the child born preterm?
- Are there any cardiac symptoms of:
  - heart failure (breathlessness, poor feeding, faltering growth, cold hands and feet)?
  - cyanosis?
  - neonatal collapse?
- Is it an asymptomatic heart murmur found on routine examination?
- Is there a syndrome such as Down syndrome?
- Is there any family history of congenital heart disease?
- Did the mother have any illnesses or take any medication during pregnancy?

## **Examination**

- Introduce yourself to mother and patient. Ask if you can examine the child.
- Position child according to age:
  - For a 6 year old – at an angle of 45°
  - For a toddler – upright on mother's knee
  - For a baby – flat on the bed
- Remove clothes from chest
- Stand back and look for:
  - Dysmorphism
  - Intravenous infusion cannula
  - Obvious cyanosis or scars.



The following examinations should be performed.

## Heart failure

The delivery of oxygen to the peripheral vascular bed is insufficient to meet the metabolic demands of the child. Usually because of left-to-right shunt with good heart pump function.

- A thin, malnourished child (faltering growth)
- Excessive sweating around the forehead
- Tachycardia
- Breathlessness  $\pm$  subcostal or intercostal recession
- Poor peripheral perfusion with cold hands and feet
- A large liver
- Never found with ventricular septal defect (VSD) or other left-to-right shunt in first week of life
- An emergency if found up to 7 days of age. Implies a duct-dependent lesion, e.g. hypoplastic left heart syndrome or coarctation

## Cyanosis

- Mild cyanosis is not visible – use the pulse oximeter

## Clubbing

- Visible after 6 months old
- First apparent in the thumbs or toes
- Best demonstrated by holding thumbs together, back to back to demonstrate loss of normal nail-bed curvature
- Disappears a few years after corrective surgery

## Pulse

- Rate (count for 6 seconds  $\times$  10)
- Rhythm (only ‘regular’ or ‘irregular’, need ECG for ‘sinus rhythm’)
- Character at the antecubital fossa with the elbows straight, using the thumbs – on both arms together

## Head and neck

- Anaemia – for older children only – ask the patient to look up and examine the conjunctivae (not appropriate in a baby).
- Cyanosis – the tongue should be examined for central cyanosis. If in doubt ask the child to stick out their tongue and ask the mother to do the same. This will detect oxygen saturations of  $<85\%$ .
- Jugular venous pressure – the head is turned towards the candidate so that the other side of the neck (the left side) can be seen with the jugular venous pressure visible, outlined against the pillows. In a child who is under 4 years, the jugular venous pressure should not be assessed.

- Carotid thrill – essential part of the examination, midway up the left side of the neck, felt with the thumb, proof of the presence of aortic stenosis

## **Precordium**

### **Inspection**

- Respiratory rate
- Median sternotomy scar (= open heart surgery – see [Section 9](#))
- Lateral thoracotomy scar (Blalock–Taussig [BT] shunt, patent ductus arteriosus [PDA] ligation, pulmonary artery [PA] band, coarctation repair)
- Additional scars, e.g. on the abdomen

### **Palpation**

- Apex beat ‘the most inferior and lateral position where the index finger is lifted by the impulse of the heart’. Place fingers along the fifth intercostal space of both sides of chest (for dextrocardia) and count down apex position only if patient is lying at 45°
- Left ventricular heave
- Right ventricular heave at the left parasternal border
- Thrills at upper or lower left sternal edge

### **Auscultation**

- Heart sounds and their character
- Additional sounds
- Murmurs, their character, intensity and where they are best heard

## **Heart sounds**

First heart sound is created by closure of the mitral and then tricuspid valves. It is not important for the candidate to comment on the nature of the first heart sound.

Second heart sound, however, is more important, created by closure of first the aortic and then the pulmonary valves.

- Loud pulmonary sound – pulmonary hypertension
- Fixed splitting of second sound (usually with inspiration the sounds separate and then come together during expiration). Listen when patient is sitting up, at the mid-left sternal edge in expiration:
  - Atrial septal defect
  - Right bundle-branch block
- Single second sound in transposition of great arteries (TGA), pulmonary atresia or hypoplastic left heart syndrome
- Quiet second sound may occur in pulmonary valve stenosis or pulmonary artery band

## **Additional sounds**

Added sounds present may be a normal third or fourth heart sound heard in the neonate or these sounds can be pathological, for example in a 4 year old with a dilated cardiomyopathy and heart failure. An ejection click is heard at aortic valve opening, after the first heart sound, and is caused by a bicuspid aortic valve in most cases.

## **Murmurs**

Before listening for any murmurs, the candidate should have a good idea of the type of congenital heart disease, which is being dealt with. The candidate should know whether the child is blue (and therefore likely to have tetralogy of Fallot) or is breathless (likely to have a left-to-right shunt) or has no positive physical findings before auscultation of the murmurs (and therefore more likely to either be normal, have a small left-to-right shunt or mild obstruction). By the time the murmurs are auscultated, there should only be two or three diseases to choose between, with the stethoscope being used to perform the fine tuning. It is best to start at the apex with the bell, and move to the lower left sternal edge with the diaphragm. Then on to the upper left sternal edge and upper right sternal edge both with the diaphragm. Additional areas can be auscultated, but provide little additional information. Murmurs are graded out of six for systolic: 1 = very soft, 2 = soft, 3 = moderate, 4 = loud with a thrill, 5 = heard with a stethoscope off the chest, 6 = heard as you enter the room. Murmurs are out of four for diastolic: 1–4 as above, no grades 5, 6.

### **Ejection systolic murmur**

Upper sternal edge – implies outflow tract obstruction. Right or left ventricular outflow tract obstruction can occur at valvar (+ ejection click), subvalvar or supra-valvar level:

- Upper right sternal edge (carotid thrill) = aortic stenosis
- Upper left sternal edge (no carotid thrill) = pulmonary stenosis or atrial septal defect (ASD)
- Mid/lower left sternal edge = innocent murmur (see below)
- Long harsh systolic murmur + cyanosis = tetralogy of Fallot

### **Pansystolic murmur**

- Left lower sternal edge ( $\pm$  thrill) = VSD
- Apex (much less common) = mitral regurgitation
- Rare at left lower sternal edge ( $\pm$  cyanosis) = tricuspid regurgitation (Ebstein anomaly)

### **Continuous murmur**

- Left infraclavicular ( $\pm$  collapsing pulse) = persistent arterial duct
- Infraclavicular (+ cyanosis + lateral thoracotomy) = BT shunt
- Any site (lungs, shoulder, head, hind-quarter) = arteriovenous fistula

### **Diastolic murmurs**

- Unusual in childhood
- Left sternal edge/apex ( $\pm$  carotid thrill or VSD) = aortic regurgitation
- Median sternotomy ( $\pm$  PS (pulmonary stenosis) murmur) = tetralogy of Fallot, repaired
- Apical ( $\pm$  VSD) = mitral flow/(rarely stenosis)

Note that listening to the back gives little diagnostic information, but is useful thinking time.

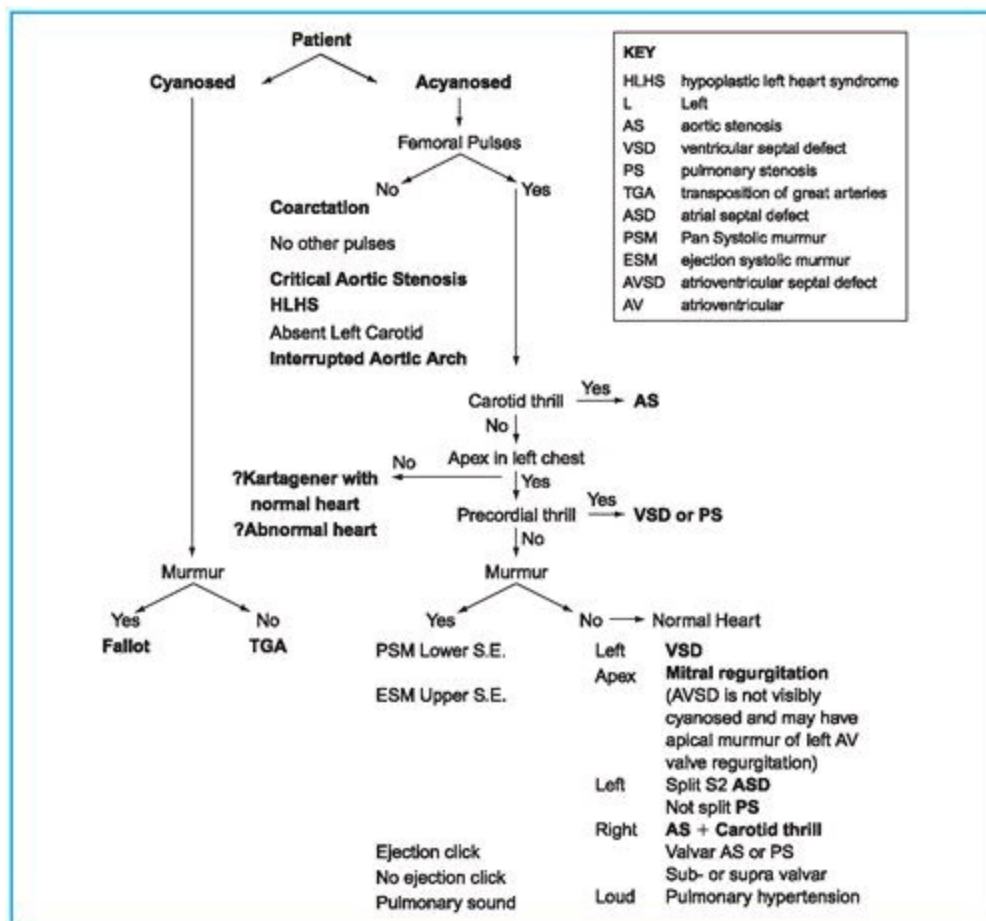
## **Presentation of findings**

Few candidates pay enough attention to the case presentation. This should be done after the examination is complete. The candidate should stand, look the examiner in the eye, and put hands behind his or her back and present. The important positives and negatives should be stated quickly and succinctly with no ‘umms’ or ‘errrs’. It is important to judge the mood of the examiner, if he or she is looking bored, then go faster. Practise with a tape recorder or video recording.

To complete the examination you would:

- Measure the blood pressure
- Measure the oxygen saturation
- Feel the femoral pulses
- Feel the liver edge

The presentation should be rounded off with the phrase ‘the findings are consistent with the diagnosis of . . .’.



Algorithm for clinical examination.

## The patient with surgical scars

- Left lateral thoracotomy:
  - PA band Thrill + ejection systolic murmur at upper left sternal edge
  - Coarctation ± left brachial pulse
  - Shunt Blue + continuous murmur
  - PDA No signs
- Right lateral thoracotomy:
  - Shunt Blue + continuous murmur
- Median sternotomy:
  - Any intracardiac operation

## 1.6 Innocent murmurs

The most common murmur heard in children is the functional, innocent or physiological heart murmur (40% of all children). They are often discovered in children with an intercurrent infection or with anaemia. These all relate to a structurally normal heart but can cause great concern within the family. There are several different types depending on the possible site of their origin. It is clearly important to make a positive diagnosis of a normal heart. The murmur should be:

- Soft (no thrill)
- Systolic
- Short, never pansystolic
- Asymptomatic
- Left Sternal edge

It may change with posture.

Diastolic murmurs are not innocent.

An innocent murmur is not associated with abnormal or added heart sounds.

Types of innocent murmur include:

- Increased flow across branch pulmonary artery – this is frequently seen in preterm neonates, is a physiological finding and resolves as the pulmonary arteries grow. The murmur disappears after a few weeks of age, and never causes symptoms
- A Still murmur – this is vibratory in nature and is found at the mid-left sternal edge. It may be caused by turbulence around a muscle band in the left ventricle
- Venous hum – it may be easy to hear the venous blood flow returning to the heart, especially at the upper sternal edge. This characteristically occurs in both systole and diastole and disappears on lying the child flat

## 2. BASIC CARDIAC PHYSIOLOGY

### 2.1 Physiology of adaptation to extrauterine life

During the adaptation from fetal life there are a number of changes in the normal child:

- A fall in the pulmonary vascular resistance, rapidly in the first few breaths, but this continues until 3 months of age
- A resultant fall in the pulmonary arterial pressure
- Loss of the placenta from the circulation
- Closure of the ductus venosus
- Closure of the ductus arteriosus
- Closure of the foramen ovale

The arterial duct is kept patent with prostaglandins  $E_1$  or  $E_2$  infusion in children with duct-dependent circulation such as transposition of the great arteries, or pulmonary atresia.

### 2.2 Physiology of congenital heart disease

The main principles of congenital heart disease are:

- The pressure on the left side of the heart is usually higher than that on the right
- Any communication between atria, ventricles or great arteries leads to a left-to-right shunt
- Pulmonary vascular resistance falls over the first 12 weeks of life, increasing the shunt

- There will only be cyanosis if the desaturated blood shunts from the right to left side
- Common mixing leads to cyanosis and breathlessness
- Duct-dependent conditions usually present at 2 days of life
- Prostaglandin E<sub>2</sub> or E<sub>1</sub> can be used to reopen the duct up to about 2 weeks of life

## 2.3 Physiology of heart muscle and heart rate

**Arterial pulse volume** depends on stroke volume and arterial compliance.

- Small pulse volume in:
  - Cardiac failure
  - Hypovolaemia
  - Vasoconstriction
- Large pulse volume in:
  - Vasodilatation
  - Pyrexia
  - Anaemia
  - Aortic regurgitation
  - Hyperthyroid
  - CO<sub>2</sub> retention
- Pulsus paradoxus:
  - Exaggeration of normal rise and fall of blood pressure with respiration, seen in airways obstruction, such as asthma
- Sinus arrhythmia:
  - Variation of the normal heart rate with respiration. Faster in inspiration and slower in expiration. Can be very marked in children

**Cardiac output** is increased by:

- Adrenergic stimulus
- Increased stretch (Starling curve)
- Increased preload
- Reduced afterload

## 3. LEFT-TO-RIGHT SHUNT

(Pink ± breathless)

### General principles

No signs or symptoms on first day of life because of the high pulmonary vascular resistance. Later, at 1 week, infant can develop symptoms and signs of heart failure.



Symptoms of heart failure:

- Tachypnoea
- Poor feeding, Faltering growth
- Cold hands and feet
- Sweating
- Vomiting

Signs of heart failure:

- Thin
- Tachypnoea
- Displaced apex
- Dynamic precordium
- Apical diastolic murmur
- Hepatomegaly

### 3.1 Atrial septal defect (ASD)

#### Types of defect

- Secundum ASD
- Primum ASD (partial atrioventricular septal defect)
- Sinus venosus ASD
- Other

#### Secundum ASD

A defect in the centre of the atrial septum involving the fossa ovalis.

#### Clinical features

- Asymptomatic
- 80% of ASDs
- Soft systolic murmur at upper left sternal edge
- Fixed split S2 (difficult to hear)

#### ECG

- Partial right bundle-branch block (90%)
- Right ventricle hypertrophy

#### Chest X-ray

- Increased pulmonary vascular markings

## **Management**

- Closure at 3–5 years (ideally)
- 90% undergo device closure in catheter laboratory
- 10% undergo surgical closure (too large or personal preference)

## **Partial atrioventricular septal defect (primum ASD)**

A defect in the lower atrial septum, involving the left atrioventricular valve which has three leaflets and tends to leak.

## **Clinical features**

- Asymptomatic
- 10% of ASDs
- Soft systolic murmur at upper left sternal edge
- Apical pansystolic murmur (atrioventricular valve regurgitation)
- Fixed split S2 (difficult to hear)

## **ECG**

- Partial right bundle-branch block (90%)
- Right ventricle hypertrophy
- Superior axis

## **Chest X-ray**

- Increased pulmonary vascular markings

## **Management**

- Closure at 3–5 years
- All require surgical closure (because of the need to repair valve)

## **Sinus venosus ASD**

A defect at the upper end of the atrial septum, such that the superior vena cava (SVC) overrides the atrial septum. The right pulmonary veins are usually anomalous and drain directly into the SVC or right atrium adding to the left-to-right shunt.

## **Clinical features**

- Asymptomatic or heart failure
- 5% of ASDs
- Soft systolic murmur at upper left sternal edge
- Fixed split S2 (easily heard)

## ECG

- Partial right bundle-branch block
- Right ventricle hypertrophy

## Chest X-ray

- Increased pulmonary vascular markings
- Cardiomegaly

## Management

- Closure at 1–5 years
- All require surgical closure and repair to the anomalous pulmonary veins

There are other rare types of ASD, which are similarly treated.

## 3.2 Ventricular septal defect (VSD)

### Small defect

A defect anywhere in the ventricular septum (peri-membranous or muscular, can be inlet or outlet). Restrictive defects are smaller than the aortic valve. There is no pulmonary hypertension.

### Clinical features

- Asymptomatic (80–90%)
- May have a thrill at left lower sternal edge
- Loud pansystolic murmur at lower left sternal edge (the louder the murmur, the smaller the hole)
- Quiet P2

## ECG

- Normal

## Chest X-ray

- Normal

## Management

- Review with echocardiography
- Spontaneous closure, but may persist to adult life

## Large defect

Defects anywhere in the septum. Large defects tend to be the same size or larger than the aortic valve. There is always pulmonary hypertension.

## Clinical features

- Symptomatic with heart failure after age 1 week
- 10–20% of VSDs
- Right ventricular heave
- Soft or no systolic murmur
- Apical mid-diastolic heart murmur
- Loud P2

## ECG

- Biventricular hypertrophy by 2 months (see [Section 15](#))

## Chest X-ray

- Increased pulmonary vascular markings
- Cardiomegaly

## Management

- Initial medical therapy, diuretics  $\pm$  captopril + added calories
- Surgical closure at 3–5 months

## 3.3 Persistent ductus arteriosus (PDA)

There is persistence of the duct beyond 1 month after the date the baby should have been born.

## Clinical features

- Asymptomatic usually, rarely have heart failure
- Continuous or systolic murmur at left infraclavicular area

## ECG

- Usually normal
- If large, have left ventricle volume loading (see [Section 15](#))

## Chest X-ray

- Usually normal
- If large, have increased pulmonary vascular markings

## Management

- Closure in cardiac catheter laboratory with coil or device at 1 year
- If large, surgical ligation age 1–3 months

Note the presence of an arterial duct in a preterm baby is not congenital heart disease. If there is a clinical problem, with difficulty getting off the ventilator, or signs of heart failure with bounding pulses, the problem is usually treated with indometacin or ibuprofen (<34 weeks). If medical management fails, surgical ligation is undertaken.

## 3.4 Aortopulmonary window

A defect in the wall between the aorta and pulmonary artery.

## Clinical features

- Rare
- Usually develop heart failure
- Continuous murmur as for PDA

## ECG

- If large, have left ventricle volume loading (see [Section 15](#))

## Chest X-ray

- If large, have increased pulmonary vascular markings

## Management

- If large, surgical ligation age 1–3 months

### 3.5 Others

There are other rare causes of significant left-to-right shunt, such as arteriovenous malformation. These are all individually rare. Medical and surgical treatment is similar to that for large ducts or VSDs.

#### Summary of left to right shunts

Disease	Symptoms	Treatment
ASD	Minimal	Surgery/catheter device at 3–5 years
VSD	None	None (in 80–90% of cases)
	Moderate	Diuretics/captopril/added calories then review early
	Severe	Surgery at 3–5 months (10–20% cases)
PDA	None	Coil or device occlusion at cardiac catheter (at 1 year old)
	Moderate/severe	Surgery, especially in preterm babies
Others rare (AP window, etc.)		Surgery at 3–4 months

### 4. RIGHT-TO-LEFT SHUNT

(Cyanosed)

#### General principles

Cyanosis in a newborn can be caused by:

- Cardiac problems (cyanotic heart disease)
- Respiratory problems (diaphragmatic hernia, etc.)
- Metabolic problems (lactic acidosis, etc.)
- Infections (pneumonia, etc.)

Cardiac cases that present on days 1–3 are usually duct dependent:

- Transposition of great arteries (common)
- Tetralogy of Fallot with pulmonary atresia (less common)
- Pulmonary atresia with intact ventricular septum (PA/IVS) (rare)
- Tricuspid atresia or other complex hearts (rare)
- Ebstein anomaly (rare)

#### Investigations

- Chest X-ray (to exclude lung pathology and large ‘wall-to-wall’ heart in Ebstein anomaly)
- Blood culture (to exclude infection)
- ECG (superior axis in tricuspid atresia)

- Hyperoxia test, 10 min in 100% O<sub>2</sub> + blood gas from right radial arterial line. If  $PO_2 > 20$  kPa then it is not cyanotic heart disease – **you must not use a saturation monitor, because this is notoriously inaccurate in the presence of acidosis**
- Echocardiogram is not first line but should be considered early on

## Management

- Resuscitate first
- Ventilate early
- Prostaglandin E<sub>1</sub> or E<sub>2</sub> infusion (5–20 ng/kg per min) (may cause apnoeas)
- Transfer to cardiac centre
- Treat as for specific condition

### 4.1 Tetralogy of Fallot

**Ventricular septal defect + subpulmonary stenosis + overriding aorta + right ventricular hypertrophy (RVH)**

#### Clinical features

- Asymptomatic usually, rarely have severe cyanosis at birth, worsens as they get older
- Loud, harsh murmur at upper sternal edge day 1
- Do not usually develop heart failure

#### ECG

- Normal at birth
- RVH when older

#### Chest X-ray

- Usually normal
- If older have upturned apex (boot shaped) + reduced vascular markings

## Management

- 10% require BT shunt in newborn if severely cyanosed
- Most have elective repair at 6–9 months

### 4.2 Transposition of the great arteries

Aorta is connected to the right ventricle, and pulmonary artery is connected to the left ventricle. The blue blood is therefore returned to the body and the pink blood is returned to the lungs. These children have high pulmonary blood flow and are severely cyanosed, unless there is an ASD, PDA or VSD to allow mixing.

## **Clinical features**

- Cyanosed when duct closes
- No murmur usually
- Can be very sick, unless diagnosed antenatally
- May be associated with VSD, coarctation or pulmonary stenosis (PS)

## **ECG**

- Normal

## **Chest X-ray**

- Normal (unusual to detect ‘egg-on-side’ appearance)
- May have increased pulmonary vascular markings

## **Management**

- Resuscitate as above
- 20% require balloon atrial septostomy at a cardiac centre (usually via umbilical vein – see [Section 17](#))
- Arterial switch operation usually before 2 weeks

## **4.3 Pulmonary atresia**

### **Duct-dependent pulmonary atresia**

#### **Clinical features**

- Cyanosed when duct closes
- No murmur usually
- Can be very sick, unless diagnosed antenatally
- May have IVS or VSD

#### **ECG**

- Normal



## **Chest X-ray**

- Normal at birth (unusual to diagnose 'boot-shaped' heart, until much older)
- Decreased pulmonary vascular markings

## **Management**

- Resuscitate as above
- BT shunt inserted surgically
- Radiofrequency perforation of atretic valve – if appropriate

## **Pulmonary atresia with VSD and collaterals**

Collaterals are abnormal arterial connections direct from the aorta to the lung substance.

## **Clinical features**

- Not usually duct dependent
- No murmur usually
- Usually present with heart failure at 1 month but may present with cyanosis at any age if collaterals are small

## **ECG**

- Biventricular hypertrophy

## **Chest X-ray**

- Boot-shaped heart
- Cardiomegaly
- Increased pulmonary vascular markings if in heart failure, or reduced vascular marking if severely cyanosed

## **Management**

- Diuretics, if in failure
- Further imaging with cardiac catheter or magnetic resonance imaging (MRI)
- Staged surgical repair

## **4.4 Ebstein anomaly**

The tricuspid valve is malformed such that it leaks, and is set further into the right ventricle than normal.

## Clinical features

- Cyanosed at birth
- Loud murmur of tricuspid regurgitation
- Can be very sick
- May be associated with maternal lithium ingestion

## ECG

- May have a superior axis

## Chest X-ray

- Massive cardiomegaly (wall-to-wall heart)
- Reduced pulmonary vascular markings

## Management

- Resuscitate as above
- Pulmonary vasodilator therapy (ventilation, oxygen, etc., see [Section 12](#))
- Try to avoid surgical shunt insertion, in which case prognosis is poor

## 4.5 Eisenmenger syndrome

This is secondary to a large left-to-right shunt (usually VSD or AVSD (atrioventricular septal defect)) where the pulmonary hypertension leads to pulmonary vascular disease (increased resistance) over many years. Eventually the flow through the defect is reversed (right to left) so the child becomes blue, typically at 15–20 years of age.

## Clinical features

- Cyanosed in teenage life
- Uncommon
- Usually secondary to untreated VSD or AVSD
- No murmur usually
- Develop right heart failure eventually

## ECG

- Severe RVH + strain

## Chest X-ray

- Decreased pulmonary vascular markings

## Management

- Supportive
- May need diuretic and anticoagulant therapy
- Oxygen at night, consider other therapy (see Pulmonary hypertension, [Section 12](#))
- Consider heart/lung transplantation

## Summary of right-to-left shunts

Disease	Symptoms	Treatment
Fallot	Loud murmur	Surgery at 6–9 months
TGA (transposition of great arteries)	No murmur	Septostomy at diagnosis (20%)
	Neonatal cyanosis	Arterial switch at <2 weeks
Pulmonary atresia (duct dependent)	No murmur	BT shunt or radiofrequency
	Neonatal cyanosis	perforation
Pulmonary atresia (VSD + collaterals)	No murmur	Staged surgical repair
	Heart failure/cyanosis	
Ebstein anomaly	Loud murmur of tricuspid regurgitation	Pulmonary vasodilatation (O <sub>2</sub> , NO, etc.)
	Cardiomegaly	
Eisenmenger syndrome	Severe cyanosis	Pulmonary vasodilators
	No murmur, loud P2	Diuretics
		Transplantation

## 5. MIXED SHUNT

(Blue and breathless)

### General principles

- Tend to present either antenatally (most often) or at 2–3 weeks. Symptoms are that of mild cyanosis and heart failure
- Includes most of the complex congenital heart diseases

### 5.1 Complete atrioventricular septal defects

There is an atrial and ventricular component to the defect, so there is pulmonary hypertension as with a large VSD. There is a common atrioventricular valve with five leaflets, not a separate mitral and tricuspid valve.

### Clinical features

- May be cyanosed at birth

- No murmur usually at birth, may develop in first few weeks
- Often present on routine echo screening (neonatal Down syndrome)
- May present with heart failure at 1–2 months

## ECG

- Superior axis
- Biventricular hypertrophy at 2 months of age
- Right atrial hypertrophy (tall P wave)

## Chest X-ray

- Normal at birth
- Increased pulmonary vascular markings and cardiomegaly after 1 month

## Management

- Treat increased pulmonary vascular resistance at birth if blue
- Treat as for large VSD if in failure (diuretics, captopril, added calories)
- Surgical repair at 3–5 months

## 5.2 Tricuspid atresia

There is no tricuspid valve and usually the right ventricle is very small.

## Clinical features

- Cyanosed when duct closes if duct dependent
- No murmur usually
- Can be very well at birth

## ECG

- Superior axis
- Absent right ventricular voltages
- Large P wave

## Chest X-ray

- May have decreased or increased pulmonary vascular markings

## Management

- BT shunt inserted surgically if very blue
- PA band if in heart failure
- Hemi-Fontan after 6 months of age (see [Section 9.2](#))
- Fontan at 3–5 years of age

## 5.3 Others

There are many other types of complex congenital heart disease.

- Common arterial trunk
- Double inlet left ventricle
- Total or partial anomalous pulmonary venous connection (unobstructed)
- Right or left atrial isomerism  $\pm$  dextrocardia

Individually, these are quite rare and their management is variable, depending on the pulmonary blood flow, the sizes of the two ventricles, etc. For further information a larger textbook of congenital heart disease should be consulted.

## 6. OBSTRUCTION IN THE WELL CHILD

(Neither blue nor breathless)

### General principles

- Often present to general practitioner with murmur
- Asymptomatic

### 6.1 Aortic stenosis

The aortic valve leaflets are fused together, giving a restrictive exit from the left ventricle. There may be two or three aortic leaflets.

### Clinical features

- Asymptomatic
- Always have a carotid thrill
- Ejection systolic murmur at upper sternal edge
- May be supravalvar, valvar (and ejection click) or subvalvar
- Quiet A2 (second heart sound aortic component)

### ECG

- Left ventricular hypertrophy

## **Chest X-ray**

- Normal

## **Management**

- Review with echocardiography
- Balloon dilate when gradient reaches 64 mmHg across the valve

## **6.2 Pulmonary stenosis**

The pulmonary valve leaflets are fused together, giving a restrictive exit from the right ventricle.

## **Clinical features**

- Asymptomatic (not cyanosed)
- May have a thrill at upper left sternal edge
- Ejection systolic murmur at upper sternal edge from day 1
- May be supralvalvar, valvar (ejection click) or subvalvar
- Quiet P2

## **ECG**

- Right ventricular hypertrophy

## **Chest X-ray**

- Normal

## **Management**

- Review with echocardiography
- Balloon-dilate when gradient reaches 64 mmHg across the valve

## **6.3 Adult-type coarctation of the aorta**

Not duct-dependent, this gradually becomes more severe over many years.

## Clinical features

- Rare
- Asymptomatic
- Always have systemic hypertension in the right arm
- Ejection systolic murmur at upper sternal edge
- Collaterals at the back
- Radiofemoral delay

## ECG

- Left ventricular hypertrophy

## Chest X-ray

- Rib-notching
- ‘3’ sign, with a visible notch on the chest X-ray in the descending aorta, where the coarctation is

## Management

- Review with echocardiography
- Stent insertion at cardiac catheter when gradient reaches 64 mmHg, or surgery via a lateral thoracotomy

## 6.4 Vascular rings and slings

Embryological remnant of aortic arch and pulmonary artery development.

## Clinical features

- Often present with stridor
- May have no cardiac signs or symptoms

## ECG

- Normal

## Chest X-ray

- May have lobar emphysema as a result of bronchial compression

## Management

- Diagnose with barium/Gastrografin swallow
- Review with echocardiography
- Additional imaging often required (computed tomography, magnetic resonance imaging, angiography)
- Surgical treatment

## 7. OBSTRUCTION IN THE SICK NEWBORN

### General principles

- Present when duct closes or antenatally
- Often have normal ECG and chest X-ray when first present
- Must feel pulses!!

### 7.1 Coarctation of the aorta

Duct-dependent narrowing, the ductal tissue encircles the aorta and causes an obstruction when the duct closes.

### Clinical features

- Very common diagnosis
- Often diagnosed antenatally
- Absent femoral pulses
- Should be born in a cardiac centre
- If not detected antenatally, presents as sick infant with absent femoral pulses
- No murmur, usually
- Signs of right heart failure (large liver, low cardiac output)
- May be breathless and severely acidotic
- Associated with VSD and bicuspid aortic valve

### ECG

- Normal

### Chest X-ray

- Normal, or cardiomegaly with heart failure

### Management



- Resuscitate
- Commence prostaglandin E<sub>1</sub> or E<sub>2</sub> (5–20 ng/kg per min)
- Ventilate early (before transfer to cardiac centre)
- Surgery 24 hours later, usually through a left lateral thoracotomy, to resect the narrow segment, unless the whole aortic arch is small, in which case the surgery is performed via a median sternotomy on bypass.

## 7.2 Hypoplastic left heart syndrome

A spectrum of disorders where the mitral valve, left ventricle and/or the aortic valve are too small to sustain the systemic output.

### Clinical features

- Common diagnosis (200–400 born annually in UK)
- Usually diagnosed antenatally
- Should be born in a cardiac centre
- If sick, presents with absent femoral + brachial pulses
- No murmur
- Signs of right heart failure (large liver, low cardiac output)
- May be breathless and severely acidotic
- Anatomy varies from mitral stenosis to mitral and aortic atresia

### ECG

- Absent left ventricular forces

### Chest X-ray

- Normal, or cardiomegaly with heart failure

### Management

- Resuscitate
- Commence prostaglandin E<sub>1</sub> or E<sub>2</sub> (5–20 ng/kg/per min)
- Ventilate early (before transfer to cardiac centre)
- Surgery (see [Section 9.3](#)) 3–5 days later

## 7.3 Critical aortic stenosis

Critical means duct-dependent, i.e. there is not enough flow across the stenotic valve to sustain the cardiac output.

## Clinical features

- Rare diagnosis
- Usually diagnosed antenatally
- Should be born in a cardiac centre
- If sick, presents with absent femoral + brachial pulses
- No murmur
- Signs of right heart failure (large liver, low cardiac output)
- May be breathless and severely acidotic
- Poor prognosis

## ECG

- Left ventricular hypertrophy

## Chest X-ray

- Normal, or cardiomegaly with heart failure

## Management

- Resuscitate
- Commence prostaglandin E<sub>1</sub> or E<sub>2</sub> (5–20 ng/kg per min)
- Ventilate early (before transfer to cardiac centre)
- Balloon dilatation 24 hours later, may require cardiac surgery

## 7.4 Interruption of the aortic arch

A gap in the aortic arch, which may occur at any site from the innominate artery around to the left subclavian artery. It is always duct-dependent.

## Clinical features

- Rare diagnosis
- Presents with absent left brachial + femoral pulses
- No murmur
- Heart failure (large liver, low cardiac output)
- Breathless and severely acidotic
- Associated with VSD and bicuspid aortic valve
- Associated with 22q11.2 deletion and DiGeorge syndrome (see [Section 10.5](#))

## ECG

- Normal

## **Chest X-ray**

- Normal, or cardiomegaly with heart failure

## **Management**

- Resuscitate
- Commence prostaglandin E<sub>1</sub> or E<sub>2</sub> (5–20 ng/kg per min)
- Ventilate early (before transfer to cardiac centre)
- Surgery 24 hours later

## **7.5 Total anomalous pulmonary venous connection**

The pulmonary veins have not made the normal connection to the left atrium. Instead they can drain up to the innominate vein (supracardiac), to the liver (infracardiac) or to the coronary sinus (intracardiac).

## **Clinical features**

- Uncommon diagnosis
- Not a duct-dependent lesion
- If obstructed, presents day 1–7 with cyanosis and collapse
- No murmur
- Signs of right heart failure (large liver, low cardiac output)
- May be breathless and severely acidotic
- May, however, present later up to 6 months of age if unobstructed, with murmur or heart failure

## **ECG**

- Normal in neonate
- RVH in older child

## **Chest X-ray**

- Normal, or small heart
- ‘Snowman in a snowstorm’ or ‘cottage loaf’ because of visible ascending vein and pulmonary venous congestion. Appearance usually develops over a few months

## **Management**

- Resuscitate (ABC)
- Ventilate early (before transfer to cardiac centre)
- Prostaglandin not effective if obstructed pulmonary veins
- Emergency surgery if obstructed

## Summary of obstructed hearts

Disease	Symptoms	Treatment
Coarctation	Absent femoral pulses	Surgery at 24 hours
Hypoplastic left heart	+ Absent brachial pulses	Norwood 3–5 days
Interrupted aortic arch	+ Absent left brachial	Surgery >24 hours
Critical aortic stenosis	+ Absent brachial pulses	Balloon >24 hours
Total anomalous pulmonary venous connection	Cyanosed, sick if obstructed	Emergency surgery

## Overview

Left-to-right shunt	Right-to-left shunt	Mixed	Well obstructions	Sick obstructions
VSD ASD PDA	Fallot TGA Eisenmenger	AVSD	AS PS	TAPVC HLHS AS CoA Int Ao Arch

There are other causes in each column, but these are less common and are unlikely to appear in examinations.

VSD, pansystolic murmur at LLSE

ASD, ejection systolic murmur at ULSE + fixed split S2

Partial AVSD, ASD + apical pansystolic murmur of mitral regurgitation

PDA, continuous murmur under left clavicle ± collapsing pulses

Tetralogy of Fallot, blue + harsh long systolic murmur at ULSE

TGA, no murmur. Two-thirds have no other abnormality, never in examinations

Eisenmenger syndrome, 10 years old ± Down syndrome, often no murmurs, loud P2

Complete AVSD, never in examinations

AS, ejection systolic murmur at URSE + carotid thrill

PS, ejection systolic murmur at ULSE ± thrill at ULSE

TAPVC/HLHS/AS/CoA/Interrupted aortic arch, never in clinical exam, but common in vivas, grey cases, data; present in first few days of life. May see postoperative cases

Key: AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation; HLHS, hypoplastic left heart syndrome; Int Ao Arch, interrupted aortic arch; LL/LRSE, lower left/right sternal edge; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of great arteries; UL/RSE, upper left/right sternal edge; VSD, ventricular septal defect

## 8. NON-BYPASS SURGERY FOR CONGENITAL HEART DISEASE

Non-bypass surgery is performed by means of a lateral thoracotomy, right or left. The scar is found

underneath the right or left arm, the anterior border of the scar tends to end under the axilla and may not be seen from the front of the chest. It is imperative that the arms are lifted and the back inspected as a routine during clinical examination otherwise the scars will be missed.

## **8.1 Shunt operation**

- Right or left modified BT shunt
- Modified shunts will mean an intact brachial pulse on that side
- Most likely to be for tetralogy of Fallot with pulmonary atresia
- If there is no median sternotomy, the infant will still be cyanosed
- Definitive repair will be performed usually by age 18 months

## **8.2 Coarctation of the aorta repair**

- May have absent left brachial pulse (subclavian flap technique) or a normal left brachial pulse
- May have no murmur and normal femoral pulses

## **8.3 Pulmonary artery band**

- Uncommon operation these days
- Usually for complex anatomy which may be palliated in the neonatal period
- There may be a thrill at the upper left sternal edge
- When present, the child is cyanosed
- The band is usually removed at 1–2 years old as part of the next procedure

## **8.4 Arterial duct ligation**

- Rare except for the ex-preterm neonate
- No murmurs and no abnormal pulses
- Usually not associated with other defects

# **9. BYPASS SURGERY FOR CONGENITAL HEART DISEASE**

Any child who undergoes open cardiac surgery, cardiopulmonary bypass, placement of a central shunt or repair of the proximal aortic arch will need a median sternotomy. Therefore any repair of intracardiac pathology will need to be performed via a midline incision.

## **9.1 Switch operation**

- Performed for transposition of the great arteries
- Undertaken before 2 weeks of age (if no VSD present)
- Involves cutting aorta and pulmonary artery and changing them round
- Have to relocate coronary arteries as well
- Mortality rate is low now, around 1%
- Outcome is affected by presence of associated defects, such as VSD, coarctation, abnormal coronary artery patterns

## 9.2 Fontan

- Any child with a complex heart arrangement that is not suitable for a repair with two separate ventricles will end up with a Fontan operation. If the pulmonary blood flow is too low at birth (cyanosis), they will have a BT shunt. If the pulmonary blood is too high (heart failure) they will have a PA band. If physiology is balanced, then conservative treatment will be undertaken until the hemi-Fontan is performed
- At about 6–8 months, the venous return from the head and neck is routed directly to the lungs. A connection is therefore made between the superior vena cava and the right pulmonary artery. The hemi-Fontan (or a Glenn or cavopulmonary shunt) is performed on bypass, via a median sternotomy. Following the operation, the oxygen saturations will typically be 80–85%
- At 3–5 years, there will be insufficient blood returning from the head to keep the child well. Hence a Fontan operation will be performed, where a channel is inserted to drain blood from the inferior vena cava up to the right pulmonary artery. This means that the child will be almost pink, saturations around 90–95%
- When completely palliated, the ventricle pumps pink oxygenated blood to the body, whereas the blue deoxygenated blood flows direct to the lungs

## 9.3 Norwood

- Used to palliate hypoplastic left heart syndrome
- Stage I at 3–5 days of age:
  - Pulmonary artery sewn to aorta so that right ventricle pumps blood to body, branch pulmonary arteries are isolated.
  - Atrial septectomy so that pulmonary venous blood returns to right ventricle
  - BT shunt from innominate artery or a conduit from right ventricle to pulmonary arteries
- Stage II (hemi-Fontan) at 5–6 months old
- Stage III (Fontan) at 3–5 years old
- Results of survival to 5 years are approximately 70–80%
- Unknown long-term results

## 9.4 Rastelli

- Used for TGA/VSD/PS
- Left ventricle is channelled through VSD to aorta
- VSD is closed with a patch of Gortex material
- Right ventricle is connected to pulmonary artery with a homograft (donor artery)
- Homograft is replaced every 20 years

## 9.5 Other operations

- A child with median sternotomy scar and lateral thoracotomy scar with a systolic and diastolic murmur at the left sternal edge:
  - This is typical of a child who has undergone insertion of a BT shunt, and then had complete repair for tetralogy of Fallot
- The child with Down syndrome who has a murmur at the left lower sternal edge and a median sternotomy scar:
  - Atrioventricular septal defect or ventricular septal defect, who has undergone repair and who has a residual ventricular septal defect – the child may also have residual left atrioventricular valve (i.e. mitral) regurgitation with systolic murmur at the apex
- Bikini incision – in girls, for cosmetic reasons who have undergone closure of atrial septal defect
- Groin puncture site – it may be worth inspecting the area of the right and left femoral vein to look for the small puncture scar of previous cardiac catheterization, for example for balloon dilatation of pulmonary stenosis

For further information, consult a larger textbook (see [Section 19](#)).

## 10. SYNDROMES IN CONGENITAL HEART DISEASE

### General principles

- Septal defects are the most common
- Anomalies of kidneys, vertebra or limbs are often connected with cardiac disorders
- Genetic causes of many syndromes now known

### 10.1 Isomerism

- Genetic defect – multifactorial, several candidates isolated

### Right atrial isomerism

#### Heart defects

- Both atria are morphological right atria
- May have apex to right (dextrocardia)
- Must have anomalous pulmonary venous connection (no left atrium to connect to)
- May have complex anatomy, with AVSD, pulmonary atresia, etc.

### **Associated defects**

- Asplenia (penicillin prophylaxis)
- Midline liver
- Malrotation of small bowel
- Two functional right lungs

## **Left atrial isomerism**

### **Heart defects**

- Both atria are morphological left atria
- May have anomalous pulmonary venous connection
- May have complex with AVSD, etc.

### **Associated defects**

- Polysplenia (usually functional)
- Malrotation (less often than in right isomerism)
- Two functional left lungs

## **10.2 Trisomy**

### **Down syndrome**

- Genetic defect – trisomy 21

### **Heart defects**

- 30% have CHD
- Usually VSD and AVSD
- All offered surgery with low risk

### **Associated defects**

- Diagnosed antenatally – increased nuchal translucency

### **Edward syndrome**



- Genetic defect – trisomy 18

### **Heart defects**

- VSD
- Double outlet right ventricle

### **Associated defects**

- Rocker-bottom feet
- Crossed index finger
- Developmental delay

### **Patau syndrome**

- Genetic defect – trisomy 15 or 13

### **Heart defects**

- VSD
- Double-outlet right ventricle

### **Associated defects**

- Holoprosencephaly
- Midline facial cleft
- Renal anomalies

## **10.3 Williams syndrome**

- Genetic defect – 7q11.23 deletion including elastin gene *ELN*

### **Heart defects**

- Supravalve aortic stenosis
- Peripheral pulmonary artery stenosis

### **Associated defects**

- Gene abnormality on long arm of chromosome 7
- Hypercalcaemia
- Serrated teeth

- Carp-shaped mouth
- Hypertelorism
- Cocktail party chatter

## 10.4 Noonan syndrome

- Genetic defect – *PTPN11* mutation (or a small number of others)

### Heart defects

- Hypertrophic cardiomyopathy
- Pulmonary valve stenosis
- ASD

### Associated defects

- Almond-shaped eyes and shallow orbits
- Shield-shaped chest, widely spaced nipples
- Short
- Not ‘male Turner’, can be girls

## 10.5 DiGeorge syndrome

- Genetic defect – 22q11.2 deletion

It is increasingly recognized that DiGeorge syndrome may not always occur with the classic form of hypocalcaemia, absent thymus, lymphopenia, cardiac defect and characteristic facies (CATCH 22). Chromosomal abnormalities have been recognized in partial cases, or even in those with familial VSD or tetralogy of Fallot (22q11.2 deletion). Deletions of the chromosome are detected using fluorescent *in situ* hybridization (FISH) probes.

### Heart defects

- Conotruncal anomalies
- Common arterial trunk
- Interrupted aortic arch
- Tetralogy of Fallot
- Familial VSD

### Associated defects

- 22q11.2 deletion

- Only have full DiGeorge syndrome if there is deletion + heart + two out of three of:
  - Cleft palate
  - Absent thymus (T cells low)
  - Absent parathyroids, hypocalcaemia
- Small jaw, small head, pinched nose, hypertelorism
- Small baby, slow development
- Renal anomalies (20%)

## Physical examination

Features to describe or exclude in this syndrome are as follows:

- Dysmorphic features of face, skull or pelvis
- Exclude cleft palate
- Check spine for scoliosis
- Check males for hypospadias

## Investigations

- Full blood count and film (ask for haematologist's report)
- Calcium and magnesium levels
- Thyroid function tests
- Check total CD4 count
- Measure total immunoglobulin E levels
- Chest X-ray
- Thymic ultrasound
- If abnormal: T-cell precursors and response to tetanus, *Haemophilus influenzae* type b (Hib) and pneumococcus vaccination

## Medical treatment (if T-cell deficient)

- Maintenance co-trimoxazole (if lymphocyte count  $<1.5 \times 10^9/l$ )
- Regular immunoglobulin
- Cytomegalovirus-negative, irradiated blood until immunological status is known
- No live vaccines, but with component or fixed vaccines

## 10.6 Alagille syndrome

- Genetic defect – jagged 1 gene (*JAG1*) mutations in 70%

## Heart defects

- Peripheral pulmonary artery stenosis

## Associated defects

- Prominent forehead; wide-apart, deep-set eyes
- Small, pointed chin
- Butterfly vertebra
- Intrahepatic biliary hypoplasia – jaundice
- Embryotoxon (slit lamp for cornea)
- Kidney, growth, abnormalities of development, high-pitched voice

## 10.7 Turner syndrome

- Genetic defect – XO

## Heart defects

- Coarctation of the aorta

## Associated defects

- Webbed neck
- Short stature
- Shield-shaped chest, wide-spaced nipples
- Infertility

## 10.8 Marfan syndrome

## Heart defects

- Aortic root dilatation (may rupture in later teenage life)
- Aortic regurgitation
- Mitral valve prolapsed
- Mitral regurgitation

## Associated defects

- *FBNI* gene mutation on chromosome 16, or *TGFBR2* mutation
- Dural ectasia
- High arched palate
- Arm-span greater than height
- Hypermobility
- Lens dislocation

- Pectus excavatum

Patients have to be managed with regular echocardiography to detect if cardiac surgery is required. The operations can be delayed by the use of  $\beta$ -blocker medication or angiotensin receptor-2 blockers, to keep the blood pressure as low as reasonable. Neonatal Marfan syndrome is particularly severe.

## 10.9 VACTERL

### Heart defects

- VSD
- Tetralogy of Fallot
- Coarctation
- PDA

### Associated defects

- Vertebral
- Anorectal
- Cardiac
- Tracheo-oEsophageal fistula
- Renal/Retardation
- Limb

## 10.10 Holt–Oram/TAR (thrombocytopenia and absent radius) (TAR)/Fanconi syndromes

- Genetic defect for Holt–Oram syndrome – 12q2 mutations

### Heart defects

- ASD

### Associated defects

- Radial aplasia
- Limb abnormalities

## 10.11 CHARGE

## Heart defects

- VSD
- Tetralogy of Fallot

## Associated defects

- Coloboma
- Heart
- Atresia choanae
- Renal/retardation
- Genital/growth
- Ear

## 10.12 Pentalogy of Cantrell

### Heart defects

- Tetralogy of Fallot

### Associated defects

- Absent sternum
- Absent pericardium
- Absent diaphragm
- Absent heart (ectopic, on the front of the chest)
- Absence of normal heart (tetralogy of Fallot)

## 10.13 Dextrocardia

A clinical diagnosis with the apex beat in the right chest. It is dangerous to use in cardiology because it gives no information about the connections or orientation of the heart. For example, if the right lung was collapsed and there was a tension pneumothorax on the left, it would be possible to find the apex beat in the right chest. However, the child would not suddenly have developed a cardiac anomaly. We use the term 'apex to right' to imply the orientation of the heart and then talk about the connections such as situs inversus (right atrium is on the left and left atrium is on the right) or some other situs.

In practice, most children with dextrocardia have a normal heart. This is most often the case when the liver is on the left. It may be part of Kartagener syndrome (primary ciliary dyskinesia) where the organs failed to rotate properly during embryological development. It is easily diagnosed by performing nasal brushings to look at the dynein arms of the cilia on electron microscopy. Associated with bronchiectasis, sinus occlusion and infertility.

If the child is blue with dextrocardia, there is almost always complex heart disease with right atrial isomerism (see above).

## 10.14 Other syndromes

### **Cri-du-chat syndrome**

- Genetic defect – 5p–
- Heart defects – VSD, ASD

### **Tuberous sclerosis**

- Genetic defect – *TSC1* and *TSC2* genes
- Heart defects – cardiac rhabdomyoma which reduce in size with age

### **Hypertrophic obstructive cardiomyopathy**

- Genetic defect – multiple genes, e.g. *MYH7*
- Heart defects – obstruction in left ventricle may be associated with Noonan syndrome and many more. In general, cardiac defects may be associated with other defects. The most common cardiac defect is a septal defect (ASD or VSD).

## 11. SYNCOPE IN CHILDHOOD

Syncope in childhood is very common. Most episodes are benign, not dangerous and are the result of neurocardiogenic syncope. Most of the investigations are of limited use and most often, it is reassurance that is needed. A suggested protocol follows for the paediatrician.

- Careful history – is syncope associated with a drop in blood pressure on standing
- Known groups of causes are:
  - Neurally mediated syncope, including postural hypotension, is most common. Tend to have prodrome with dizziness on standing, or sitting upright. Nausea, vomiting and pallor before loss of tone and consciousness
  - Cardiovascular causes, including arrhythmia, structural and vascular
  - Non-cardiovascular pseudo-syncope, including psychogenic
- Investigations:
  - ECG, 12-lead. Exclude long Q–T interval, pre-excitation or heart block
- If there is a good history of neurally mediated syncope, then no further tests are required, but if very frequent or severe attacks, then refer to a cardiologist for Tilt testing
- If there are some warning bells, such as exercise-related symptoms, then:
  - Exercise ECG if the symptoms relate to exercise

- Cardiac event monitoring (longer than 24-hour) or reveal implantation
- Electroencephalogram is rarely helpful
- Management, in increasing complexity:
  - Reassurance, advice to stand slowly and sit down if dizzy
  - Encourage to drink more water and take more salt
  - Fludrocortisone 50–100 µg/day
  - $\beta$  Blocker

## 12. PULMONARY HYPERTENSION

For children, pulmonary hypertension is when the systolic pulmonary artery pressure is higher than 50% systemic systolic pressure. Needless to say this is normal in the 1-day-old baby, but is abnormal after that time.

Classification of pulmonary hypertension	
<b>1 Pulmonary arterial hypertension (PAH)</b>	
1.1 Idiopathic	
1.2 Heritable	
1.2.1 BMPR2	
1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)	
1.2.3 Unknown	
1.3 Drugs and toxins induced	
1.4 Associated with (APAH)	
1.4.1 Connective tissue diseases	
1.4.2 HIV infection	
1.4.3 Portal hypertension	
1.4.4 Congenital heart disease	
1.4.5 Schistosomiasis	
1.4.6 Chronic haemolytic anaemia	
1.5 Persistent pulmonary hypertension of the newborn	
<b>1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis</b>	
<b>2 Pulmonary hypertension due to left heart disease</b>	
2.1 Systolic dysfunction	
2.2 Diastolic dysfunction	
2.3 Valvular disease	
<b>3 Pulmonary hypertension due to lung diseases and/or hypoxia</b>	
3.1 Chronic obstructive pulmonary disease	



- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

#### **4 Chronic thromboembolic pulmonary hypertension**

#### **5 PH with unclear and/or multifactorial mechanisms**

- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 = activin receptor-like kinase 1 gene; APAH = associated pulmonary arterial hypertension; BMPR2 = bone morphogenetic protein receptor, type 2; HIV = human immunodeficiency virus; PAHV = pulmonary arterial hypertension.

## **12.1 Persistent pulmonary hypertension of the newborn**

### **Aetiology**

A relatively uncommon scenario, there are numerous causes, most commonly:

- Structural lung disease (e.g. congenital diaphragmatic hernia)
- Respiratory distress syndrome (hyaline membrane disease)
- Group B streptococcal infection
- Idiopathic

### **Diagnosis**

- Persistent hypoxia
- Low cardiac output
- Loud P2 on examination
- Oligaemic lung fields
- Hepatomegaly
- Episodic desaturation, preceding a fall in blood pressure
- Echocardiographic appearance of pulmonary hypertension:
  - High-velocity tricuspid regurgitation jet
  - Dilated right ventricle

- Right-to-left shunt via atrial septum
- Long right ventricle ejection time
- High-velocity pulmonary regurgitation jet
- Right-to-left shunt via arterial duct

## Treatment

- Good ventilation (high O<sub>2</sub>, low CO<sub>2</sub>)
- Use oscillation ventilation if necessary
- Sedation with morphine or fentanyl
- Paralysis
- Good chest physiotherapy
- Restricted fluids
- Pharmacology:
  - Nitric oxide (5–20 ppm, inhaled)
  - Prostacyclin (50 ng/kg, nebulized each 15 minutes)
  - Magnesium sulphate (200 mg/kg intravenous)
- Extracorporeal membrane oxygenation (ECMO) as last resort

## 12.2 Increased pulmonary blood flow

Post-tricuspid shunts:

- Ventricular septal defect
- Arterial duct
- Common arterial trunk
- Aortopulmonary window

## Treatment

- Repair defect by 3 months of age to avoid irreversible pulmonary vascular disease

## 12.3 Chronic hypoxia

### Aetiology

- Bronchopulmonary dysplasia
- High altitude
- Cystic fibrosis
- Upper airway obstruction
- Chronic bronchiectasis

## Investigation

- Sleep studies
- ECG (right ventricular hypertrophy)
- Ear/nose/throat opinion (upper airway obstruction)
- Chest X-ray
- Echocardiogram
- Cardiac catheterization with pulmonary vascular resistance study

## Treatment

- Ensure good airway mechanics
- Treat underlying cardiac condition if appropriate
- Added O<sub>2</sub> to keep O<sub>2</sub> saturations >94%
- Maintain low CO<sub>2</sub> (consider night-time ventilation)
- If responsive to vasodilators:
  - Nifedipine (0.1 mg/kg three times a day)
  - Dipyridamole (2.5 mg/kg 12 hourly)
  - Nebulized or intravenous prostacyclin
- Consider heart/lung transplantation if appropriate

## 12.4 Pulmonary venous hypertension

### Aetiology

- Uncommon
- Mitral valve stenosis (rare in children)
- Total anomalous pulmonary venous connection
- Pulmonary vein stenosis
- Hypoplastic left heart syndrome

Investigation and treatment are determined by aetiology.

## 13. DRUG THERAPY FOR CONGENITAL HEART DISEASE

### 13.1 Heart failure

- Diuretics (furosemide (frusemide) and spironolactone or amiloride)
- Captopril
- Added calories
- Note that digoxin not routinely used now in left-to-right shunt

## 13.2 Anticoagulation

- Aspirin – for arterial platelet aggregation prevention orally (5 mg/kg per day)
- Heparin – for arterial anticoagulation, intravenous
- Warfarin – for venous or arterial thrombus prevention
- Streptokinase – for thrombolysis
- Tissue plasminogen activator – for thrombolysis

## 13.3 Pulmonary hypertension

- Oxygen – therapeutic vasodilatation
- Low CO<sub>2</sub> – good ventilation
- Alkalosis – bicarbonate if needed
- Dipyridamole – increases cyclic guanosine monophosphate (cGMP) levels
- Amlodipine – only if proven to tolerate it
- Nitric oxide – 2–20 ppm
- Prostacyclin – nebulized (Iloprost) or intravenous
- Bosentan – endothelin receptor (ET<sub>A</sub> and ET<sub>B</sub>) antagonist
- Sildenafil – increases cGMP levels

## 13.4 Antiarrhythmia

### Supraventricular tachycardia (SVT)

- Vagal manoeuvres first
- Adenosine intravenous 50–250 µg/kg
- DC synchronized cardioversion 0.5–2 J/kg

### Ventricular tachycardia (VT)

- Cardioversion if pulse present – synchronized 0.5–2 J/kg
- Defibrillation if no pulse – 2–4 J/kg

### Prophylaxis for arrhythmias

This tends to be very variable from unit to unit. Suggestions are:

- SVT – flecainide, sotalol, digoxin or propranolol
- VT – flecainide, sotalol, amiodarone (toxic side effects on thyroid, skin and lungs)

# 14. ACQUIRED HEART DISEASE

## 14.1 Kawasaki disease

### Clinical features

- Fever >5 days
- Plus at least four of:
  - Rash
  - Lymphadenopathy
  - Mucositis (sore mouth, strawberry tongue)
  - Conjunctivitis
  - Extremity involvement (red fingers/toes)
- ± coronary artery aneurysms (25% of untreated cases, 4.6% of treated cases)
- ± abdominal pain, diarrhoea, vomiting, irritable, mood change, hydrops of gallbladder, peeling extremities, thrombocytosis

### Pathology

- Marked similarity to toxic shock syndrome
- Perhaps immune response to disease or toxin

### Investigation

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood count (WBC), blood culture, antistreptolysin O test (ASOT), viral, throat swab, ECG

### Heart

- Pericardial effusion
- Myocardial disease (poor contractility)
- Endocardial disease (valve regurgitation)
- Coronary disease:
  - Ectasia, dilatation
  - Small, 3–5 mm, aneurysms – resolve
  - Medium, 5–8 mm, aneurysms – usually resolve
  - Giant, >8 mm, aneurysms – ischaemia later

Greatest risk if male, <1 year, fever >16 days, ESR >100, WBC >30 000

Echocardiogram at 10–14 days, 6 weeks, 6 months or longer if abnormal.

### Treatment

- Immunoglobulin 2 g/kg over 12 hours
- Aspirin 30 mg/kg per day (four times per day dosage) reduce to 5 mg/kg per day when fever resolves
- Continue aspirin until 6 weeks or longer if abnormal echocardiogram

## 14.2 Dilated cardiomyopathy

### History

- Multiple transfusions, recent viral illness, family history of myopathy or autoimmune diseases. Consider nutritional deficiencies (e.g. selenium, thiamine)

### Examination

- Full cardiovascular examination
- Exclude myopathy

### ECG

- Evidence of ischaemia
- Arrhythmias – unrecognized tachycardia

### Echocardiogram

- Exclude anomalous coronary artery

### X-ray

- Look for arterial calcification

### Blood

- Metabolic:
  - Carnitine (and acylcarnitine) profile
  - Amino acids, organic acids, lactate
  - Creatinine and electrolytes (including phosphate)
  - Liver function tests and lactate dehydrogenase, membrane-bound creatine kinase
  - Selenium and thiamine
- Autoimmune:
  - Antinuclear, anti-DNA antibodies; immune complexes
- Virology:
  - Full blood count, ESR, CRP,
  - Polymerase chain reaction for Epstein–Barr virus, Cocksackievirus, adenoviruses, echoviruses

- Stools for viral culture

Other investigations include abdominal ultrasound for arterial calcification, electromyography and muscle biopsy if there is myopathy. Rare causes include endomyocardial fibrosis, tropical diseases, amyloid.

## 14.3 Hypertrophic cardiomyopathy

### History

Family history of sudden unexplained death, cardiomyopathy or myopathy. If a neonate, check if an infant of diabetic mother, or if mother was given ritodrine. Hypertrophy is more suggestive of metabolic cause compared to dilated cardiomyopathy. Consider inherited causes.

### Examination

- Exclude syndromes, Noonan syndrome, Leopard syndrome, Friedreich ataxia, neurofibromatosis, lipodystrophy
- Exclude endocrine disease, thyroid (hyper- and hypo-), acromegaly
- Exclude hypertension; check for gross hepatomegaly
- Check for cataracts, ophthalmoplegia, ataxia, deafness, myopathy
- Look for signs of mucopolysaccharidoses

### Echocardiogram

- Exclude tumours, amyloid, endocardial infiltration

### ECG

- Look for short PR + giant complexes (Pompe syndrome)
- Look for QRS–T axis dissociation (Friedreich ataxia)

### Blood tests

- Carnitine (decreased) + acylcarnitine profile
- Creatine phosphokinase (increased = glycogen storage disease type III)
- Blood film for vacuolated lymphocytes, if positive check white cell enzymes (suggesting storage disorders)
- Calcium (hyperparathyroidism)
- Thyroid function tests, fasting blood sugar
- Lactate, amino acids

### Urine

- Glycosaminoglycans (for mucopolysaccharidosis)
- Organic acids
- Vanillylmandelic acid

If no cause is found, screen family for hypertrophic obstructive cardiomyopathy (HOCM) and consider a gene probe for HOCM

## 14.4 Suspected bacterial endocarditis

All children and adults with congenital, and many with acquired, heart disease are no longer given antibiotic prophylaxis before dental extraction and potentially septic procedures in the UK.

### History

- If a child is admitted with an unexplained fever, has or might have congenital heart disease, has murmurs (? changing), suspect bacterial endocarditis
- Ask for history of recent boils, sepsis, dental extraction, etc.
- Suspected bacterial endocarditis may be found postoperatively following insertion of prosthetic material such as homograft or prosthetic valve

### Examination

- Full cardiovascular examination
- Hepatosplenomegaly, fever, heart sounds and signs of infected emboli: Osler nodes, Roth spots, septic arthritis, splinter haemorrhages, haematuria, nephrosis

### Investigations

- Six blood cultures from different sites at different times over 2 days, using the most sterile technique possible, but do not clean blood culture bottles with alcohol (or else the organisms will be killed off)
- Full blood count, ESR, CRP, ASOT throat swab
- Echocardiogram and ECG
- Consider ventilation–perfusion scan, white cell differential
- Urine test for blood
- Dental opinion

### Treatment

- If proven, treatment is for 6 weeks, predominantly intravenous
- Blood antibiotic levels may be taken for back titration after stabilization on antibiotic regimen – this will be used to assess that there is sufficient antibiotic present to have a bactericidal effect



- Antibiotics chosen should be those with a good record of deep-tissue penetration, e.g. fusidic acid, gentamicin

## 14.5 Rheumatic fever

- Uncommon in UK
- Increasing incidence with reduced use of antibiotics to treat sore throats
- Diagnosed by modified Duckett–Jones criteria (two major or one major + two minor criteria):
- Major criteria:
  - Carditis
  - Polyarthrititis
  - Chorea
  - Erythema marginatum
  - Subcutaneous nodules
- Minor criteria:
  - Fever
  - Arthralgia
  - Previous rheumatic fever or carditis
  - Positive acute-phase reactants (ESR, CRP)
  - Leukocytosis
  - Prolonged P–R interval

## Investigations

- ASOT
- Throat swab for group A streptococci
- ECG
- Echocardiogram (mitral regurgitation, myocarditis, pericarditis)

## Treatment

- Penicillin or cefuroxime (if sensitive)
- Prophylactic phenoxymethylpenicillin orally for 25 years

## 14.6 Pericarditis

### Aetiology

- Coxsackieviruses
- Enteroviruses
- Staphylococci
- Tuberculosis

- Oncological
- Rheumatic fever

## **Presentation**

- Chest pain (inspiratory)
- Acute collapse (effusion)
- Soft, muffled heart sounds

## **Examination**

- Pericardial friction rub
- Fever

## **ECG**

- ST elevation, convex upwards
- T-wave inversion

## **Treatment**

- Anti-inflammatory drugs (ibuprofen)
- Drain large pericardial effusion

## **15. ECG**

### **15.1 The ECG and how to read it**

Before interpreting a paediatric ECG it is essential to know the following:

- How old is the child?
- Is the ECG recorded at a normal rate (25 mm/s) and voltage (10 mm/mV)?

## **Rate**

When measuring the heart rate on the ECG, the number of large squares is counted between the R waves. The rate is calculated as  $300/\text{number of squares}$ .

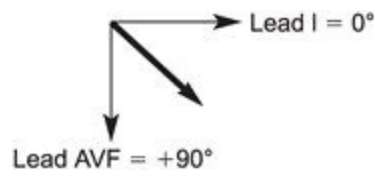
## **Rhythm**

Sinus rhythm can only be inferred if there is one P wave before each QRS and if the P-wave axis is between  $0$  and  $90^\circ$ .

# Axis

## QRS axis

This is calculated by adding the total positive deflection (R wave) and subtracting the negative deflection (Q + S wave). The resulting vector is plotted for lead I and AVF:



The P-wave and T-wave axes should be plotted similarly. This is important. For example, if there is left atrial isomerism, there is no sinoatrial node (a right atrial structure). This means that the P-wave axis is abnormal (superior) and can lead to the diagnosis. Similarly, in cardiomyopathies, such as Friedreich ataxia, there is a difference in the axis between QRS and T of more than 75°. This can help to make the diagnosis (see below).

Normal QRS axis for

- newborn – 90–180°
- 2–5 years – 45–135°
- >5 years – 10–100°

## Causes of a superior axis (>180°)

- Atrioventricular septal defect
- Tricuspid atresia
- Ebstein anomaly
- Noonan syndrome
- Wolff–Parkinson–White syndrome
- <1% of normal individuals

Note that AVSD will have right ventricular hypertrophy, whereas tricuspid atresia usually has no right ventricular forces. Either can have large P waves.

## P wave

The axis should be from 0° to 90°. The normal size is  $2 \times 2$  little squares (0.08 s, 0.2 mV). If there are not regular P waves before each QRS consider the following:

- Complete heart block – there is complete dissociation between the QRS and P waves, i.e. with no fixed relationship; see below for list of causes
- Atrial flutter – usually with 2:1 block, there is a typical saw-tooth baseline
- Inverted P waves – these are typically seen with:

- Left atrial isomerism (no RA → no sinus node)
- Postoperatively
- Occasionally in normal individuals (coronary sinus rhythm).
- Peaked P waves – seen in right atrial hypertrophy:
  - Tricuspid regurgitation (e.g. Ebstein anomaly)
  - Atrioventricular septal defect
  - Pulmonary hypertension
  - Cardiomyopathy

## **P–R interval**

Normal in children is two to four little squares (0.08–0.16 s).

### **Causes of a long P–R interval**

- Atrioventricular septal defects
- Myocarditis
- Digoxin toxicity
- Hyperkalaemia
- Duchenne muscular dystrophy
- Hypothermia
- Diphtheria

### **Causes of a short P–R interval**

- Wolff–Parkinson–White syndrome
- Pompe disease (wide QRS)
- Lown–Ganong–Levine syndrome (normal QRS)

## **Q wave**

Not often seen in paediatrics. Rare to see signs of infarct. Normal Q waves are seen in V1, V2 in young children and are allowed in other leads if small <0.2 mV.







### **Causes of Q waves**

- Dextrocardia
- Left ventricular volume overload V5, V6 (e.g. large PDA or VSD)
- Congenitally corrected transposition
- Ischaemia (Kawasaki disease, anomalous left coronary artery from pulmonary artery)
- Ischaemia postoperatively

## **QRS wave**

Normal duration is 0.08 seconds. Prolonged in right bundle-branch block, e.g. after repair of tetralogy of Fallot.

- Delta ( $\delta$ ) wave – seen in Wolff–Parkinson–White syndrome, the slurred upstroke to R wave, represents depolarization via the accessory pathway, with a short P–R interval. There will be a wide QRS and the QRS axis will be unusual, even superior. Likely to have supraventricular tachycardias (re-entry).
- R–S progression – the best way to assess ventricular hypertrophy. The following pattern should be seen:

Lead V1	Lead V6
Newborn (0–1 month)	
Dominant R 	Dominant S 
Infant (1–18 months)	
Dominant R 	Dominant R 
Adult (>18 months)	
Dominant S 	Dominant R 

Therefore, if there is persistence of the newborn pattern in an infant then right ventricular hypertrophy is suggested. Other features of hypertrophy are:

- Right ventricular hypertrophy
  - Upright T waves V1 (from 1 week to 16 years is abnormal)
  - Q wave in V1
  - R waves >20 mm in V1
- Left ventricular hypertrophy
  - Inverted T waves in V6
  - Q waves in V6
  - Left axis deviation for age
  - R waves >20 mm in V6
- Biventricular hypertrophy
  - Total voltage (R+S) in V3 or V4 of >60 mm only sign of large VSD

## Q–T interval

Measured from the start of the Q wave to the end of the T wave (U wave if present). This represents

the total time taken for depolarization and repolarization. Normal is <0.44 seconds for a heart rate of 60/min. To correct for the heart rate use the Bazett formula:

$$QT_c = QT / \sqrt{(RR)}$$

i.e. QT (corrected) = QT measured / (square root of time from R to R).

For example: if QT measured = 0.30 s at a rate of 120, then  $QT_c = 0.3 / \sqrt{(0.5)} = 0.4$  (normal).

If Q–T interval is long then abnormal T waves and a slow heart rate may result. The cause of long Q–T is thought to be differential sympathetic drive to the two sides of the ventricle, allowing one side to repolarize before the other, hence prolonging the total time of repolarization. This also explains why the T waves are abnormal.

### **Causes of long Q–T interval**

- Genetic causes of long Q–T syndrome (LQT1, LQT2, LQT3, LQT4, formerly Romano–Ward syndrome and Jervell–Lange–Nielsen syndrome and may be associated with sensorineural deafness)
- Hypocalcaemia
- Hypokalaemia
- Hypomagnesaemia
- Head injury
- Hypothermia
- Drug administration such as domperidone or erythromycin

### **S–T segment**

Unusual to get marked changes in S–T segments. May represent ischaemia in Kawasaki disease, anomalous left coronary artery from pulmonary artery and postoperative cardiac surgery.

### **T waves**

Normally T waves are downward in V1 from 1 week to 16 years of age.

T-wave axis should be within 75° of QRS. If not think of:

- Friedreich ataxia
- Dilated cardiomyopathy
- Noonan syndrome
- Long Q–T syndrome

Peaked T waves seen in hypokalaemia and digoxin toxicity.

## 15.2 Tachycardias

### Supraventricular tachycardia (SVT)

- Likely if the heart rate is  $>240/\text{min}$
- Tend to be faster rates – approximately  $300/\text{min}$
- Tend to be narrow complex ( $<0.08\text{ s}$ , unless aberrant conduction)
- Often caused by Wolff–Parkinson–White syndrome
- Respond to adenosine (intravenous rapid bolus) or vagal manoeuvres such as immersion in ice-cold water, carotid sinus massage or Valsalva manoeuvre in older children

Can use flecainide, propranolol, sotalol, esmolol, amiodarone for treatment/prophylaxis.

Do NOT use eyeball pressure, or intravenous verapamil.

For atrial flutter, adenosine challenge brings out flutter waves. Standard treatment is then to use synchronized DC cardioversion ( $1\text{ J/kg}$ )

### Ventricular tachycardia (VT)

- Tend to be slower rates – approximately  $200/\text{min}$
- Tend to be wide complex ( $>0.08\text{ s}$ )
- There is P-wave dissociation
- Can have torsade de points, which can degenerate to ventricular fibrillation
- Treatment is usually amiodarone (can use flecainide, etc.)

## 15.3 Bradycardias

### Complete heart block

Often present at birth but may be diagnosed antenatally. Baby is born (sometimes following emergency caesarean section) with heart rate of about  $70/\text{min}$  but is perfectly well. Usually needs no treatment for several years. Intervene if faltering growth, collapses, heart failure, Stokes–Adams attacks or resting heart rate  $<40/\text{min}$ . These would be indications for pacemaker insertion.

#### Causes

- Maternal systemic lupus erythematosus
- Congenitally corrected transposition of the great arteries
- Postoperative
- Myocarditis
- Rheumatic fever

# **Sick sinus syndrome**

- Tachy/brady syndrome
- May be seen after heart surgery
- Caused by scar formation over sinus node
- To be differentiated from sinus arrhythmia which is normal variation in heart rate caused by the effects of respiration

If symptomatic needs pacemaker insertion.

## **16. CHEST X-RAYS**

### **16.1 Cardiac outlines**

#### **Neonatal**

- ‘Egg-on-side’:
  - Transposition of great arteries
  - Narrow vascular pedicle (aorta in front of pulmonary artery)
- Boot-shaped:
  - Tetralogy of Fallot with pulmonary atresia
  - Pulmonary artery bay because of absent pulmonary artery
- ‘Snowman in a snowstorm’:
  - Obstructed total anomalous pulmonary venous connection
  - Small heart with pulmonary venous congestion
- Wall-to-wall heart:
  - Ebstein anomaly
  - Massive cardiomegaly with right atrial dilatation

#### **Infantile**

- Cottage loaf:
  - Total anomalous pulmonary venous connection
  - Visible ascending vein on upper left border

#### **The older child**

- Cardiomegaly with increased pulmonary vascular markings:
  - Atrial septal defect
- Small heart with pulmonary oligoemia:
  - Eisenmenger syndrome
  - Probably secondary to VSD or AVSD



## Globular heart

Usually associated with pericardial effusions, perhaps secondary to pericarditis or dilated cardiomyopathy.

## Situs

Check the heart is on the left along with the stomach bubble, and that the liver is on the right. This may be helpful in diagnosing right atrial isomerism, etc., as above.

## Oligaemic lung fields

Reduced pulmonary blood flow such as tetralogy of Fallot, Ebstein anomaly, persistent pulmonary hypertension.

## Plethoric lung fields

Left-to-right shunts, especially VSD and AVSD. Useful in transposition of the great arteries.

## Normal lung fields

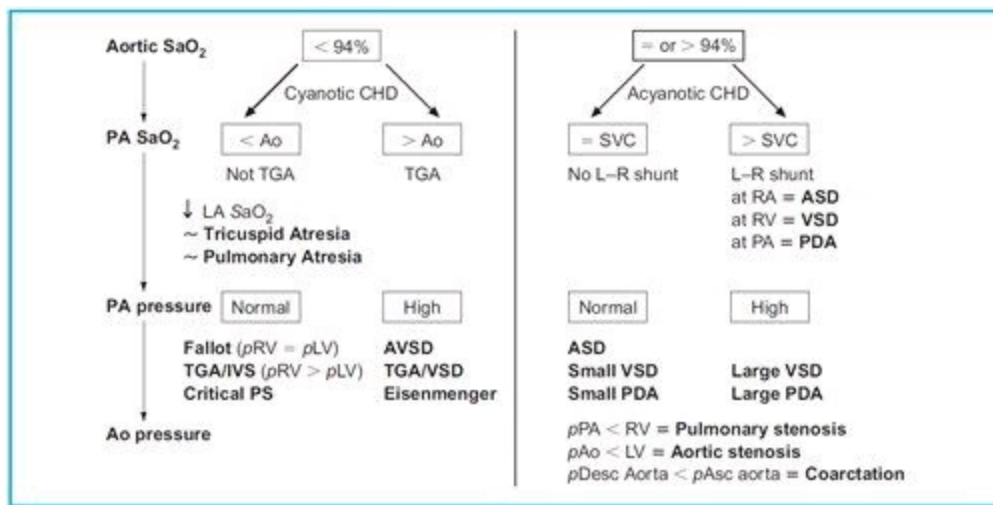
Those lesions with no shunt, such as pulmonary stenosis and aortic stenosis.

## 17. CARDIAC CATHETERIZATION

### 17.1 Diagnostic cardiac catheterization

Normal	Right atrium	Left atrium
	$\text{SaO}_2 = 65\%$	$\text{SaO}_2 = 99\%$
	Press = 4 mmHg	Press = 6 mmHg
	Right ventricle	Left ventricle
	$\text{SaO}_2 = 65\%$	$\text{SaO}_2 = 98\%$
	Press = 25/4	Press = 75/6 (age dependent)
	Pulmonary artery	Aorta
	$\text{SaO}_2 = 65\%$	$\text{SaO}_2 = 97\%$
	Press = 25/15	Press = 75/50 (age dependent)

To analyse cardiac catheter data, it is important to start with the aortic saturations. Follow the algorithm below.



## Algorithm for cardiac catheter data

- If pink (aortic  $SaO_2 \geq 94\%$ ) check pulmonary artery  $SaO_2$ . If this is greater than systemic venous  $SaO_2$ , then there is a left-to-right shunt. If it is the same as venous  $SaO_2$  then look for a pressure drop (AS/CoA).
- If blue (aortic  $SaO_2 < 94\%$ ) check pulmonary artery  $SaO_2$ . If this is greater than aortic  $SaO_2$ , then the diagnosis is transposition of the great arteries. If it is less than aortic  $SaO_2$  then the problem is not TGA. Check pulmonary artery pressure. If less than right ventricular pressure then there is right ventricular outflow obstruction, probably tetralogy of Fallot.
- True diagnostic catheterization is rarely performed, use echocardiography instead
- Usually for assessment between staged surgical operations
- Pulmonary vascular resistance assessments for left-to-right shunts to determine operability:
  - Measure pulmonary artery pressure and resistance (PVR) at baseline
  - Measure oxygen consumption for accurate determination
  - Repeat measurement in nitric oxide at two different doses
  - Repeat measurement in oxygen or prostacyclin
  - If  $PVR > 7 \text{ Wood units} \times m^2$ , then inoperable
  - If PVR falls by more than 20% then is partly reversible

## 17.2 Interventional cardiac catheterization

### Interventional cardiac catheters

Eighty per cent of cardiac catheters are used for interventional treatment:

- ASD – septal occlusion device in 90% of secundum ASD after 3 years of age
- VSD – not usually used, but may be appropriate in apical muscular VSDs
- PDA – coil or device occlusion at 1 year of age
- AS – balloon dilatation is standard treatment at any age (see above)
- PS – balloon dilatation is standard treatment at any age
- Coarctation – stent insertion in teenagers or adults
- Pulmonary atresia – radiofrequency perforation as newborn or shunt insertion surgically

- Branch PS – stent insertion in older children
- Arrhythmias – radiofrequency or cryoablation

## **Balloon atrial septostomy**

- Usually performed under echocardiographic control at the bedside in the paediatric intensive care unit
- Mostly performed in babies less than 2 days old with transposition of the great arteries (see above), who are severely cyanosed where there is insufficient mixing or where it is not possible to perform a neonatal switch operation
- May be required in other conditions, such as pulmonary atresia with intact ventricular septum
- Most are performed via the umbilical vein and the procedure only takes a few minutes
- If the child is older than 3 days, the femoral vein approach is usually required
- A catheter is passed via the vein into the right atrium and hence into the left atrium across the foramen ovale. The balloon on the end of the catheter is inflated and the balloon is withdrawn rapidly into the right atrium. This tears a hole in the atrial septum allowing blood to pass freely from right to left and vice versa.

## **18. IMAGING**

### **18.1 Echocardiography**

- Mainstay of diagnostic tools
- Doppler to assess velocity (and hence pressure gradient) across valves or VSD
- Colour flow to highlight small defects or turbulent blood flow
- Transoesophageal echo for posterior heart structures or during interventional cardiac catheterization, especially in adults with congenital heart disease
- Future uses for intravascular ultrasound, three-dimensional ultrasound and contrast echocardiography

### **18.2 Magnetic resonance imaging**

- Standard diagnostic imaging for complex diseases where echocardiogram is insufficient
- Spin-echo for routine imaging
- Contrast-enhanced for blood flow
- Three-dimensional magnetic resonance imaging for reconstruction

### **18.3 Positron emission tomography**

- Uses ammonium ion to give blood-pool images
- Best for myocardial perfusion imaging

## 18.4 Radionuclear angiography

- For quantifying left-to-right shunt (e.g. ASD)
- For determining right or left ventricle function and ejection fraction

## 19. FURTHER READING

Anderson RH, Baker EJ, Macartney FJ, Rigby ML, Shinbourne EA, Tynan M, eds (2009). *Paediatric Cardiology*, 3rd edn. London: Churchill Livingstone.

Andrews RE, Tulloh RMR (2002). Hypoplastic left heart syndrome: diagnosis and management. *Hospital Medicine* **63**:24–7.

Brogan PA, Bose A, Burgner D, et al. (2002). Kawasaki disease: an evidence-based approach to diagnosis, treatment, and proposals for future research. *Archives of Diseases in Childhood* **86**:286–90.

Park MK, Guntheroth WG (1987). *How to Read Pediatric ECGs*. Chicago, IL: Year Book Medical Publishers (still the best ECG book).

Tulloh RMR (2005). Congenital heart disease in relation to pulmonary hypertension in paediatric practice. *Paediatric Respiratory Reviews* **63**:174–80.

### Website

[www.childrens-heart-fed.org.uk](http://www.childrens-heart-fed.org.uk)

---

# Chapter 2

## Child Development, Child Mental Health and Community Paediatrics

*Joanne Philpot and Ruth Charlton*

---

## CONTENTS

### Child Development

#### 1. Developmental assessment

- 1.1 Milestones
- 1.2 Developmental assessment
- 1.3 Management of the child with global developmental delay

#### 2. Vision

- 2.1 Assessment of visual acuity
- 2.2 Squints

#### 3. Hearing

- 3.1 Assessment of auditory function

#### 4. Speech and language

- 4.1 Communication
- 4.2 Differential diagnosis of speech and language problem
- 4.3 Specific speech and language delay
- 4.4 Clinical assessment

#### 5. Autistic spectrum disorder

- 5.1 Assessment of children on the autistic spectrum

#### 6. Developmental coordination disorder

**7. Attention deficit hyperactivity disorder**

**8. Special educational needs and the educational statement**

**Child Mental Health**

**9. Chronic fatigue syndrome/Myalgic encephalopathy**

**10. Eating disorders in childhood and adolescence**

**11. Depression in childhood and adolescence**

**12. Self-harm and suicide**

**13. Schizophrenia with childhood onset**

**14. Conduct disorders**

**15. Common behavioural problems in pre-school children**

15.1 Sleep disorders

15.2 Feeding problems in infancy and childhood

15.3 Temper tantrums

15.4 Breath-holding attacks

**16. Common problems in the school-aged child**

16.1 School refusal

16.2 Non-organic abdominal pain/headache/limb pains

16.3 Sleep problems in the school-aged child

16.4 Tics

**17. Enuresis/Encopresis and soiling**

17.1 Enuresis

17.2 Encopresis

**Community Paediatrics**

**18. Child health surveillance**

18.1 Summary of newborn screening

18.2 School-aged children

**19. Immunization in childhood**

19.1 Immunization schedule

[19.2 Contraindications to immunization](#)

[19.3 Immunization reactions](#)

[19.4 Additional information on vaccines](#)

## **[20. Adoption and fostering](#)**

[20.1 Adoption](#)

[20.2 Fostering](#)

## **[21. The Children Act 1989 and Human Rights Act 1998](#)**

[21.1 Aims of the Children Act](#)

[21.2 Human Rights Act 1998](#)

## **[22. Sudden infant death syndrome and Child Death Review](#)**

## **[23. Accident prevention](#)**

## **[24. Further reading](#)**

---

# Child Development

---

## 1. DEVELOPMENTAL ASSESSMENT

This is a key part of the assessment of any child. It is important to learn the common milestones.

### 1.1 Milestones

It is important to consider the following four areas:

- 1. Gross motor
- 2. Fine motor and vision
- 3. Speech and hearing (language)
- 4. Social

### Milestones in child development

Age	Gross motor	Fine motor and vision	Language	Social
6 weeks	Head lag still present on pulling from a supine to sitting position When held in ventral suspension, head can be held in the same plane as the body	Maintains fixation and follows an object through 90° in the horizontal plane	Makes throaty noises	Smiles in response to appropriate stimuli
3 months	Able to raise head and chest on forearms in the prone position Head steady when pulled to sit	Will fix and follow an object through 180° in the horizontal plane Hands beginning to be brought to the mid-line Attempts to make contact with offered object	Vowel sounds and noises uttered on social contact Turns head to sound, level to the ear	Social smile (infant has awareness that smile attracts attention) May show displeasure on interruption of social contact
6 months	Can roll over Sits briefly or with some support	Transfers Reaches out for objects Mouthing objects	Unintelligible babble Will turn when name is called	Plays with feet Holds onto bottle when fed



<b>9 months</b>	Sits steadily Pivots to reach objects Stands holding onto objects	Looks for toy fallen from view Pokes objects with index finger	Shouts to gain attention Understands 'no' Two-syllable babble	Finger feeds Resists when objects removed
<b>12 months</b>	Crawling Pulls to stand Cruising	Pincer grip Banging bricks together	Two words with meaning Responds to 'give it to me' Shows recognition of objects by using them, e.g. brush	Waves bye bye Claps hands Empties cupboards
<b>15 months</b>	Walking well	Pincer grip refined, tiny objects can be picked up delicately Casting	Expression several words Understands words such as cup, names of brothers and sisters Jargon and jabbering Echolalia (repetition of words spoken to the child)	Drinks from a cup Indicates wants without crying, i.e. pointing, pulling, asking
<b>18 months</b>	Stoops and retrieves objects Carries toys while walking	Delicate pincer grasp Scribbles	Points to parts of body Understands up to 50 words Knows common objects by name, e.g. cat Follows one-step command, e.g. 'give me a doll' Expression 25 to 50 words	Holds spoon and gets food to mouth Into everything Takes shoes and socks off Indicates toilet needs
<b>2 years to 2.5 years</b>	Climbs and descends stairs one step at a time Kicks a ball Climbs furniture	Copies vertical line Tower of eight bricks	Uses plurals Follows two-step request, eg 'get the ball and put it in the box' Identifies objects from hearing their use Selects toy from others, i.e. 'Give me the sheep, brush'	Plays alone Eats with spoon and fork
<b>3 years</b>	Pedals tricycle Jumps well Momentarily balancing on one foot	Copies a circle Matches two colours	Knows some colours Three- to four-word sentences Name, age and sex on request Pronouns and plurals Knows more about time, today and not today Starts to tell stories	Out of nappies during the day Separates from mother easily (less apprehensive about you the candidate) Eats with knife and fork Dresses with supervision
<b>4 years</b>	Stands on one foot well Hops	Copies a cross and square Draws man with three parts	Count to 10 Identifies several colours 100s of questions Understands numbers Past tense Increasing concentration	Shares toys Out of nappies by night Brushes teeth Toilet alone
<b>5 years</b>	Walks down stairs one foot per step Bounces and catches ball	Copies triangle Draws man with six parts Writes name Do up buttons	Comprehension: 'what do you do if you are hungry, cold, tired?' Comprehension of prepositions: 'put brick on, under, in front of'; opposites: hot, cold; if elephant is big, a mouse is small definition of words, e.g. ball, banana	Chooses friends Comforts in distress Acts out role play

## 1.2 Developmental assessment

- It is important when assessing development to determine the skills achieved in the four areas
- Use a structured approach. Complete one area of development before moving on to the next

- If the child is already sitting use the opportunity to assess language, social and fine motor development. Do not disrupt the child to do gross motor tests – you may well have difficulty settling them again and in older children gross motor gives you the least additional information. Leave it to the end
- If the child is playing, WATCH. He or she will often demonstrate skills
- Start with tasks that you expect the child to be able to do. Once you have demonstrated that the child can do one level, push up to the next level until he or she is not able to perform the task, e.g. if you have demonstrated that the child can copy a square do not ask him or her to draw a circle because you have already demonstrated that the child is past this level; instead see if he or she can copy a triangle
- Work through the parents if the child is shy or apprehensive, e.g. ask the parents to draw a circle for the child to copy or test the child about colours, numbers, stories, etc
- If child does not cooperate do not panic. You can still get clues from observing. Remember stranger awareness and non-compliance are developmental milestones in themselves

There are a number of standardized assessments that can be used to more accurately determine the child's development age:

- The Griffiths Mental Development Scales
- The Bayley Scales of Infant Development
- The Schedule of Growing Skills

## 1.3 Management of the child with global developmental delay

Developmental delay can result from many causes:

- 40% have chromosomal abnormalities
- 5–10% have developmental malformations
- 4% have metabolic disorders

### Causes of developmental delay

#### Static causes

##### Prenatal

- Chromosomal abnormalities
- Intrauterine infections
- Teratogens
- Congenital brain malformations, e.g. neuronal migration defects
- Specific syndromes

##### Perinatal

- Prematurity

- Ischaemic–hypoxic encephalopathy
- Birth trauma
- Meningitis

## **Postnatal**

- Trauma
- Intracranial infections

## **Progressive causes**

### **Endocrine**

- Hypothyroidism

### **Metabolic**

- Aminoacidurias
- Galactosaemia
- Mucopolysaccharidoses
- Lesch–Nyhan syndrome

### *Degeneration of the cerebral grey matter*

- Tay–Sachs disease
- Gaucher disease
- Niemann–Pick disease
- Batten disease
- Leigh disease
- Menkes disease

### *Degeneration of the cerebral white matter*

- Krabbe disease
- Metachromatic leucodystrophy
- Canavan disease

### *Peroxisomal disorders*

- Zellweger syndrome

### **Infection**

- Subacute sclerosing panencephalitis (SSPE)

## **History**

A good history is essential to help determine the cause and appropriate investigations. Information is

required on prenatal history, perinatal history and postnatal development. Are there any associated symptoms such as seizures? General health is important when considering metabolic disorders. Family history may give the strongest clue to a chromosomal disorder. Enquire about previous pregnancy losses.

## **Examination**

A thorough examination is essential.

Neurodegenerative conditions affecting the grey matter tend to present with dementia and seizures. Conditions affecting the white matter tend to present with spasticity, cortical deafness and blindness.

### **Inspect for:**

- Sex of child – X-linked conditions such as fragile X, Menkes, Hunter and Lesch–Nyhan syndromes
- Age of the child:
  - First 6 months: Tay–Sachs disease, Leigh’s disease, infantile spasms, tuberose sclerosis
  - Toddlers: infantile metachromatic leucodystrophy, mucopolysaccharidoses, infantile Gaucher disease, Krabbe’s disease
  - Older children: juvenile Batten disease, SSPE, Wilson’s disease, Huntington disease
- Dysmorphic features: Down syndrome, mucopolysaccharidoses
- Neurocutaneous signs: ataxia telangiectasia, Sturge–Weber syndrome, incontinentia pigmenti, tuberose sclerosis
- Extrapramidal movements: cerebral palsy, Wilson’s disease, Huntington disease
- Tremor: Wilson’s disease, Friedreich’s ataxia, metachromatic leucodystrophy

### **Note growth of child**

- Large head: Alexander, Canavan and Tay–Sachs syndromes, mucopolysaccharidoses
- Small head : cerebral palsy, autosomal recessive microcephaly, Rubinstein–Taybi, Smith–Lemli–Opitz and Cornelia de Lange syndromes
- Growth pattern (e.g. faltering growth with metabolic disease, gigantism with Soto syndrome)

### **Systematic examination**

- Eyes: corneal clouding, cataract, cherry-red spot, optic atrophy
- Neurological examination including gait, scoliosis, tremor, extrapyramidal movements, tone, power and reflexes of limbs
- Associated system involvement (e.g. cardiac abnormalities, organomegaly in metabolic disease)
- Genitalia
- Hearing and vision should be checked

Further assessment often involves input from other professionals of the child development team, e.g. speech and language therapists and physiotherapists.

## **Investigations**

A thorough history and examination may lead to targeted investigations, e.g. a specific genetic test or metabolic test. For approximately 40% of cases no cause is found. The two most useful investigations are genetic studies and brain imaging.

If no specific diagnosis is suggested then consider the following.

### **Blood tests**

- Chromosomal analysis
- Thyroid function tests
- TORCH serology in infants (TORCH, toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus and herpes simplex virus)
- Plasma amino acids
- Ammonia
- Lactate
- White cell enzymes

### **Urine tests**

- Urinary organic acids
- Urinary amino acids
- Urinary mucopolysaccharidoses

### **Brain imaging**

This will identify congenital brain abnormalities and diagnose degenerative conditions such as the leucodystrophies and grey matter abnormalities.

### **EEG**

This will identify SSPE and Batten disease

## **Management**

This is multidisciplinary. A child in whom a disability has been identified will be referred to a child development team. The precise make-up of the team depends on the local resources but can include the following:

- Community paediatrician
- Speech and language therapist
- Physiotherapist
- Occupational therapist
- Child psychologist/psychiatrist
- Play therapist
- Pre-school therapist, e.g. portage
- Nursery teachers
- Health visitors
- Social workers

The role of the multidisciplinary team is to:

- identify the disability and try to determine the cause
- support the family
- liaise with education and social services as appropriate
- refer to other appropriate professionals, e.g. for genetic counselling
- provide ongoing therapy to support needs, e.g. physiotherapy, speech and language therapy

## 2. VISION

Each year around 500 children are registered blind or partially sighted. Early diagnosis is important because:

- appropriate treatment may reduce the severity of the disability or stop progression
- other medical conditions associated with visual problems can be diagnosed
- genetic counselling can be offered
- pre-school learning support can be started

### Causes of visual impairment in childhood

- Cataract
- Glaucoma
- Optic nerve:
  - Leber optic atrophy
  - Septo-optic dysplasia
  - Raised intracranial pressure, e.g. hydrocephalus
- Retinal abnormalities:
  - Retinopathy of prematurity
  - Hereditary Leber amaurosis
  - Retinoblastoma
- Amblyopia as a result of squint, refractive error or ptosis

### 2.1 Assessment of visual acuity

There is no national policy on visual screening or who should do it (primary care or orthoptists) in the UK. At present there are different screening policies in different health authorities. Visual screening is under review together with the results from trials on treatment of amblyopia.

### Current recommendations

- Newborn screening inspecting the eyes for anomalies

- Repeat eye examination at the 6-week check
- Orthoptist's assessment of all children in the 4- to 5-year age group. This is to assess acuity and to detect squints. The advantage of screening at this age is easier testing of visual acuity compared with younger children. Parents will usually recognize a squint but amblyopia as a result of refractive error will be detected only when the child's vision is assessed monocularly
- Screening very-low-birthweight babies to detect retinopathy of prematurity
- Visual screening in children with other major disabilities

Between the ages of 6 weeks and 4 years identification of visual defects will rely on concern being raised by the parents or other professionals.

## Methods of testing visual acuity

**Newborn:** inspection of the eye for cataract and other abnormalities – including red reflex

**6 weeks:** inspection of the eye. The child should also be able to fix and follow an object held at arms' length through 90° in the horizontal plane

**12 weeks:** the child should be able to fix and follow an object 180° in the horizontal and vertical planes

**10 months:** an infant can pick up a raisin. By one year they can pick up individual '100 and 1000s' sweets. If possible try to test the acuity of both eyes

**2–3 years:** test each eye individually. Various tests for visual acuity are available:

- Preferential looking test – this can be used in a child too young to identify objects. Large cards with pictures on in different positions, i.e. top right-hand corner, bottom left-hand corner, are shown to the child and the eye movements are observed as the child focuses on the picture as it moves around the card
- Picture cards – children asked to identify picture cards at a set distance. Picture size varies to determine the acuity

**3 years:** visual acuity should be assessed in each eye. By this age the Sheridan–Gardner test can usually be used. The child has a card with five letters on, the Key card. The examiner stands 6 m away and holds up a letter that the child has to identify on his card

**4 years and upwards:** by this age the child can usually verbally identify letters and therefore a Snellen chart can be used

## Refer for specialist examination

- Abnormality detected in routine examination
- Child at high risk of visual disorders:

- Child with other major disabilities
- Family history of inheritable visual disorders
- Parental concerns

## 2.2 Squints

Squints are common, occurring in approximately 4% of children. There is a strong familial incidence. A squint is usually noticed by the parents first and parental report of squint should be taken seriously.

A squint is a misalignment of the visual axis of one eye. To prevent seeing double, the image from the squinting eye is suppressed by the brain. Without treatment, this can lead to amblyopia.

A squint is either:

- latent, i.e. only there at certain times (such as fatigue, illness, stress) or
- manifest, i.e. present all the time

It is either:

- alternating – the patient uses either eye for fixation while the other eye deviates. As each eye is being used in turn, vision develops more or less equally in both or
- monocular – only one eye is used for fixation and the other eye consistently deviates. The child is more prone to develop amblyopia as the deviated eye is consistently not being used

It is either:

- convergent, i.e. turns in, or
- divergent, i.e. turns out

It is either:

- non-paralytic or
- paralytic

### **Non-paralytic squint**

This is the more common type of squint and includes the following:

- Most of the congenital and infantile convergent squints
- The accommodative convergent squint. This is the most common type of squint. The child is usually long-sighted. The degree of accommodation used to attempt to focus results in convergence of the eyes. It commonly occurs around 18 months to 2 years. In the most cases the squint can be controlled by spectacles that correct for the long-sightedness
- In a few cases a non-paralytic squint is the result of an underlying ocular or visual defect, e.g.



cataract, high refractive errors, retinopathy of prematurity, retinoblastoma

## Paralytic squints

These are the result of weakness or paralysis of one or more of the extraocular muscles. They are less common.

- The deviation worsens on gaze into the direction of action of the affected muscle
- Congenital paralytic squints are more commonly the result of developmental defects of the cranial nerves, muscle disease or congenital infection
- Acquired paralytic squints usually signify a serious pathological process, e.g. brain tumour, central nervous system infection, neurodegenerative disease

## Assessment of squint

- Ocular movements assessed to exclude paralytic squint
- Corneal reflex examined, looking for symmetry of the light reflex
- Cover/uncover test: the child sits comfortably on a parent's lap. Their attention is attracted and, while looking at an object, one of the eyes is covered. If the uncovered eye moves to fix on the object there is a squint present, a manifest squint. This may be one of the following:
  - Unilateral squint – the squinting eye takes up fixation of the object when the other eye is covered. When the cover is removed the squinting eye returns to its original squinting position
  - Alternating squint – the squinting eye takes up fixation of the object when the other eye is covered. When the cover is removed the squinting eye maintains fixation and the previously fixing eye remains in a deviated position, i.e. the squint alternates from one eye to the other
- Rapid cover/uncover test: sometimes a squint is not present all the time but only when tired or stressed. In the rapid cover test the occluder is moved quickly between the eyes. If the eye that has been uncovered moves to take up fixation there is a latent squint

## Principles of treatment for a squint

- Develop best possible vision for each eye:
  - Correct any underlying defect, e.g. cataract
  - Correct refractive errors with spectacles
  - Treat any amblyopia with occlusion therapy to encourage use of the amblyopic eye
- Achieve best ocular alignment:
  - In accommodative squints correction of long-sightedness by spectacles usually controls the excessive convergence
  - For other types of squints surgery is required. This is particularly important for congenital squints. The longer the defect persists untreated the less chance there is for development of good visual function

## 3. HEARING

Between 1 and 2 children per 1000 population have permanent childhood deafness, 84% congenital and 16% acquired. Early detection of hearing problems and treatment has permanent beneficial effects.

Hearing loss can be:

- conductive: external or middle-ear problems
- sensorineural: inner ear (cochlea) or nerve VIII problems
- mixed

## **Possible interventions**

- Hearing aids
- Cochlear implant – will allow more deaf children to develop spoken language
- Involvement of Speech and Language therapy services
- Pre-school/in-school learning support, e.g. signing

## **Routine hearing screening programme**

There is universal neonatal screening to identify deafness. The neonatal screening tests used are the otoacoustic emissions test and auditory brain-stem response testing.

### **Well baby**

- Otoacoustic emissions test

### **Special care baby**

- Otoacoustic emissions test
- Auditory brain-stem response test

If these tests are ‘not passed’ then refer for audiology assessment.

### **At pre-school entry**

A pre-school hearing test is currently performed in some areas of the UK. The screening test used is the sweep audiogram.

If the screening test is failed the child is referred to an audiologist for further assessment. Referrals to audiology can also be made at any time if concerns are raised about hearing or speech and language development, e.g. by the parents.

## **High-risk infants who should be referred on for audiology assessment**

- Babies who do not pass screening tests
- Babies with craniofacial abnormalities

- Babies with chromosomal abnormalities
- Babies diagnosed with a syndrome
- Family history of sensorineural deafness
- Babies ventilated as neonates for 5 days
- Babies with hyperbilirubinaemia to exchange level
- Babies with a congenital infection
- Babies who have received ototoxic drugs with levels outside the therapeutic range
- Babies with neonatal meningitis

### 3.1 Assessment of auditory function

- Babies:
  - Diagnostic auditory brain-stem response testing
  - Otoacoustic emissions test
- 2 years:
  - Visual reinforcement audiometry
  - Performance games
  - Speech discrimination test
  - Free-field audiometry
- 3 years and over:
  - Pure-tone audiometry

It is important to consider both the developmental and the chronological age when deciding which test to use.

#### **Automated otoacoustic emissions test**

- Measures function of inner ear
- In healthy cochlea, vibration of the hair cells in response to noise generates acoustic energy – called otoacoustic emissions
- Probe placed in ear canal and generates clicks. The energy produced is detected by a microphone within the probe
- Screen displays pass or refer – no interpretation needed
- Quick to perform:
  - Needs quiet baby
  - No debris in canal or middle ear
  - Only assesses function of ear – no assessment of neural pathway

#### **Automated auditory brain-stem response**

- Measures integrity of inner ear and the auditory pathway
- Stimulus is presented using earphones or ear canal probe. Electrophysiological response from the brain stem is detected by scalp electrodes

- Screening can be performed by non-specialist – pass/fail
- Takes 15 minutes:
  - Needs quiet baby
  - Debris in canal or middle ear can affect test

## **Visual reinforced audiometry**

Sounds are presented to the child via a loudspeaker arrangement which enables the sound to be presented precisely at different decibels (dB) for each frequency tested. If the head turns to the sound the child is rewarded by a visual stimulus, e.g. a toy lighting up in a box. Headphones can be used in a compliant child so allowing individual ears to be tested.

## **Performance test or Go games**

These tests are useful for children with an actual or developmental level of 2–4 years. They require some understanding and cooperation. The child is asked to perform a task when he or she hears a noise, i.e. put man in boat. It can be performed by health visitors.

## **Speech discrimination test**

This test is useful for children with a 2.5 years plus actual or developmental level. An example is the McCormick Toy Test. Toys are laid out in front of the child on the table and the examiner asks the child to identify the toy called. The examiner must test voice level against a sound meter. The mouth is covered to prevent lip reading and the tester has to be careful not to give visual clues. The toys are in pairs to test for consonants, e.g. duck/cup.

## **Free-field testing**

Suitable for children aged 2 years and over. It does not require understanding or cooperation so it is useful for children with developmental delay or behavioural problems. Sounds are produced within a free field at different frequencies. The child's reaction to sound is observed and assessed if satisfactory.

## **Pure-tone audiometry**

By 4 years of age a child should be able to cooperate with this test. Both ears can be tested separately. The audiometer delivers sounds at different frequencies and intensities. It is possible to determine the child's threshold at each sound frequency. It takes at least 10 minutes to perform.

## **The audiogram**

Key to symbols used:

$x$ -axis = frequency (Hz)

y-axis = hearing level (dBHL)

○ = air conduction right ear

X = air conduction left ear

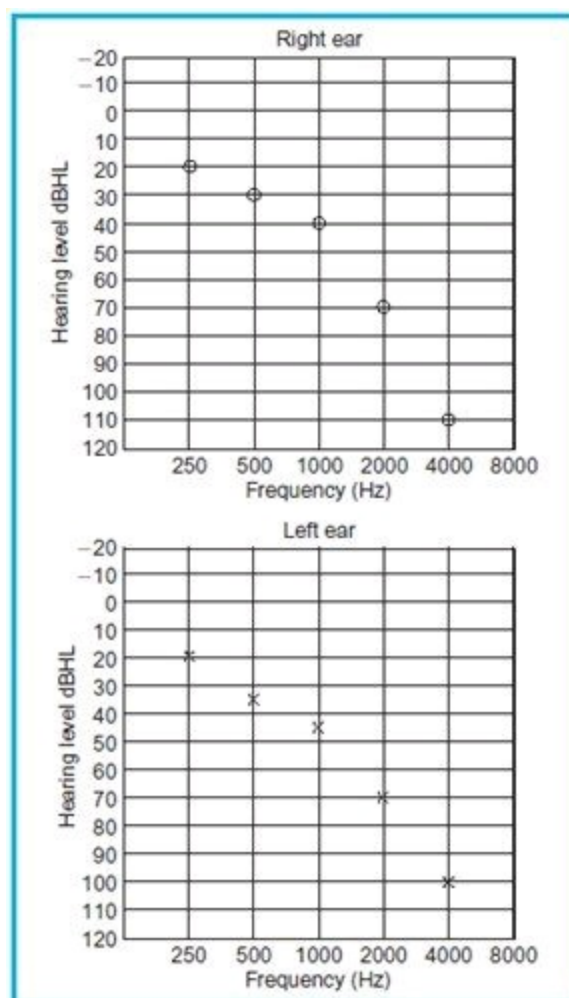
△ = bone conduction unmasked – vibrator vibrates whole skull no matter on which mastoid it is placed. Assesses both cochleas unless one ear is masked

- Air conduction assesses the whole auditory system
- Bone conduction assesses the auditory pathway from the cochlea and beyond
- If bone conduction is normal but air conduction thresholds are raised a conductive hearing loss is present
- If both bone and air conduction thresholds are raised a sensorineural hearing loss is present
- An impairment greater in air than bone conduction suggests a mixed loss

Normal range                    -10 to +20 dBHL

Moderate hearing loss    20–40 dBHL

Profound hearing loss    90–120 dBHL



High-frequency hearing loss in a child with speech delay.

## Sweep audiometry

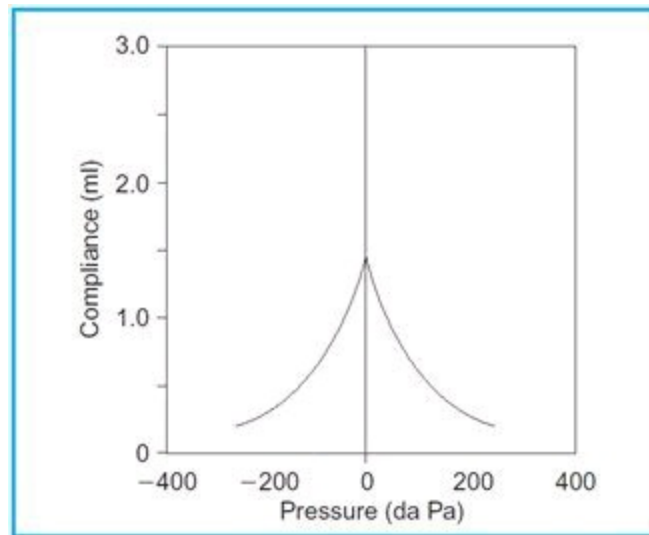
Same principle as above but quicker to perform because various sound frequencies are tested at only

one intensity (around 25 dB). It is used as a screening test at the pre-school entry. If the child fails at any frequency then full audiometry is performed.

## Tympanometry

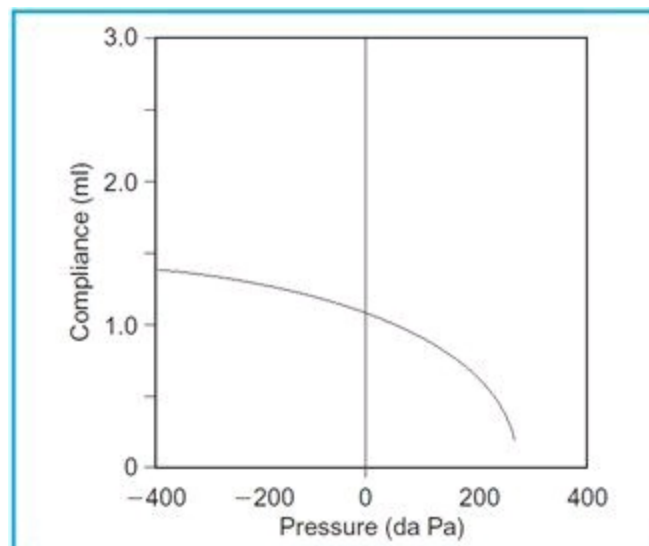
The compliance of the tympanic membrane and ear ossicles is assessed by a probe that fits snugly in the external auditory canal, which is able to generate positive and negative pressures while recording the sound reflected back from a small microphone within the probe. It is suitable for any age child, but primarily used to check for 'glue ear'. In the normal ear, the peak is at 0 pressure, reflecting the equal pressures on either side of the drum. The trace is flattened if a middle-ear effusion is present.

### Normal trace



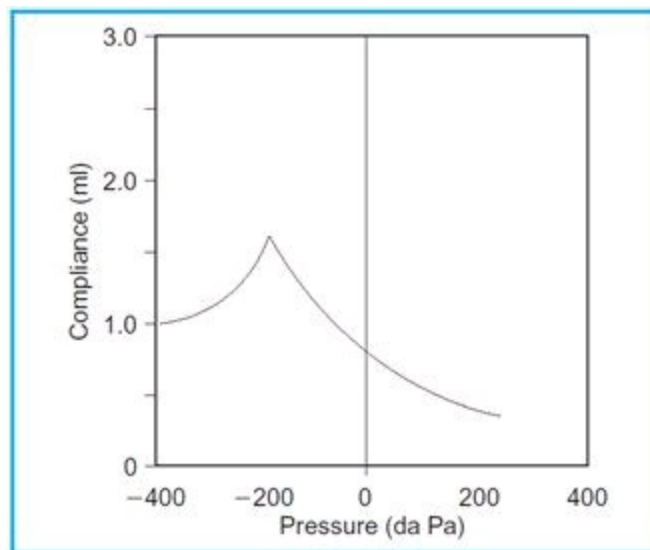
### Flattened trace with no clear peak

– middle-ear effusion



### Peak at negative pressure (shift to left)

– eustachian tube dysfunction (retracted drum)



## 4. SPEECH AND LANGUAGE

### 4.1 Communication

Acquisition of communication involves the following.

#### Speech

- Expressive – production of speech
- Comprehension – understanding what is being said
- Comprehension development is ahead of expressive development

#### Non-verbal communication

- Eye contact, pointing, body gestures

#### Social communication

- Reciprocity and sharing of communication, insight into what is socially acceptable, sharing communication, listening skills

Problems in speech and language development are very common in pre-school children (5–10%) and more common in boys.

### 4.2 Differential diagnosis of speech and language problem

#### Problem with language input

- Hearing deficit
- Reduced exposure to spoken language, e.g. social circumstances, twins, poor parenting skills

## **Problems with language processing**

- Specific speech and language delay
- Associated with general developmental delay
- Associated with reduced communicative intent and poor social skills, i.e. autistic spectrum disorder
- Associated with brain abnormalities, e.g. epilepsy, Llandau–Kleffner syndrome

## **Problems with language output**

- Neurological or muscular problems, e.g. cerebral palsy

## **4.3 Specific speech and language delay**

Most children with specific language disorders have no cause identified for their disorder. There is often a positive family history of language disorders. Many children have a mixture of problems but they can be divided as follows.

### **Problems in auditory/linguistic processing leading to difficulties with expressions**

- Phonology – articulation and making the speech sounds
- Grammar – understanding the forms and structure of language

### **Problems in understanding the appropriate meaning and use of language**

- Semantics – the meaning of words and sentences
- Pragmatics – the appropriate social use of language

## **4.4 Clinical assessment**

The role of the doctor is to determine:

- the nature of the speech and language problem
- if there are other problems such as general delay, autistic spectrum
- any underlying cause, e.g. deafness, cleft palate, neuromuscular disorder

## **Investigations**



- It is important to confirm that the hearing is normal (see earlier)
- EEG if there is a clear history of loss of language skills to exclude epilepsy syndromes
- Chromosomal studies if there are other associated difficulties

## **Management of speech and language problem**

- If speech and language delay is the only problem, it is usually managed by speech and language therapists alone without continuing paediatric input
- If there are other additional problems, multidisciplinary assessment is usually necessary, involving some or all of the multidisciplinary team
- It is also important that advice is given to education team about the child's difficulties to enable them to access the national curriculum. Children with severe difficulties are sometimes placed in language units with access to on-site speech and language therapists. The majority, however, are managed in mainstream school with a speech and language programme incorporated into their individual education plans. Speech and language therapists then review the programme intermittently

## **5. AUTISTIC SPECTRUM DISORDER**

There is a wide variation in the clinical presentation of autism (autistic spectrum disorder). It is a communication disorder. The spectrum includes classic autism through to Asperger syndrome. The prevalence of autistic spectrum disorder is around 4/1000. Boys tend to outnumber girls by 3:1. Three areas of development are affected.

### **Social skills**

- Non-verbal behaviours, e.g. eye contact, body posture
- Failure to develop peer relationships
- Lack of social and emotional sharing

### **Verbal and non-verbal communication**

- Delay in development of spoken language
- No attempt to communicate by other means
- Inability to initiate conversation
- Stereotyped and repetitive language, lack of imaginative play

### **Repetitive and stereotype patterns of behaviour**

- Adherence to routines
- Lack of imaginative play and behaviour
- Restrictive patterns of interest
- Preoccupation with parts of objects

- Repetitive motor mannerisms, e.g. hand flapping, door closing

## Other features in classic autism

- The abnormal functioning is observed in one of these areas of development before the age of 3 years
- The behaviour is not accounted for by another diagnosis. A large number of children with syndromes and chromosomal abnormalities have autistic features
- Over 50% also have associated intellectual impairment that can affect the behaviours observed
- By middle age 30% have developed epilepsy
- Hearing and visual problems are common
- Dyspraxia is common

## Asperger syndrome

- Presentation is usually after 3 years of age
- Early language appears normal
- Presentation is often via school with behavioural and social difficulties and speech and language problems
- Children are often aware that he or she is 'different' which can lead to anxiety, psychiatric morbidity and social exclusion

## 5.1 Assessment of children on the autistic spectrum

This is by multidisciplinary assessment. The format varies depending on local services but should include: a developmental paediatrician, a psychiatrist/psychologist and a speech and language therapy assessment:

- **History:** it is important to obtain a thorough history, including developmental milestones and family history. Information from other sources, e.g. nursery, is important. There are now formal scored tools to help assessment
- **Examination:** it is important to exclude other diagnoses that can present with autistic features, e.g. fragile X, tuberose sclerosis
- **Investigation:** children on the autistic spectrum often do not tolerate investigations. Chromosomes and brain imaging are more likely to yield a positive result in children with associated severe cognitive impairment. An EEG should be considered in children showing development regression

## Management

Each child needs to be assessed as an individual to determine the degree of difficulty in social and communication skills, and an individual management plan must be decided upon.

## Health

Communication with parents about their concerns and difficulties with management of the child is essential. Access to more information should be provided, e.g. the National Autistic Society. Access to psychiatric/psychology services for the individual and the family is essential.

## **Education**

Liaison with education is essential. Pre-school intervention within the home and nursery is possible with early diagnosis. Local outreach services may be available to go into the home to give management advice. Formal pre-school notification by health to education allows the child's needs to be assessed before school placement. School placement can vary from mainstream with support through to a special unit depending on the individual child. Children on the autistic spectrum often require a high teacher to pupil ratio in a highly structured environment to minimize disruptions. Speech and language input to help communication skills is also important.

## **Social services**

Living with a child on the autistic spectrum affects all members of the family. Families often need respite care and support in the home.

## **6. DEVELOPMENTAL COORDINATION DISORDER**

Developmental coordination disorder (DCD) is a common type of sensory-processing problem that causes difficulty in performing coordinated actions. The child is often described as clumsy. There may be associated problems of language, perception and thought processing. Concern about motor coordination is one of the most common reasons for a referral to a paediatrician from education. Children present with both fine- and gross-motor difficulties.

In the younger child symptoms include:

- Slow gross-motor development
- Poor motor skills, e.g. running, jumping, not able to catch a ball
- Difficulty dressing
- Poor pencil grip
- Difficulty with jigsaws
- Anxiety

In the older child symptoms include the following:

- Avoidance of physical education
- Slow school progress
- Reduced attention span
- Difficulty with maths, reading

- Trouble copying from the blackboard
- Poor writing skills
- Inability to follow instructions
- Poor organizational skills

## **Differential diagnosis**

- Learning disability
- Neuromuscular problem
- Attention-deficit hyperactivity disorder
- Specific speech and language delay
- Visual problem
- Cerebral palsy
- Brain tumour

## **Assessment**

In the pre-school child initial assessment is usually by a paediatrician to exclude other pathologies, including general developmental delay. The school-age child is usually assessed by a paediatrician, but information should also be obtained from the school about the child's difficulties and overall progress. In addition, often a speech and language assessment and occupational therapy assessment are required.

The occupational therapist examines:

- fine- and gross-motor developmental levels
- visual motor integration (e.g. doing puzzles or copying shapes)
- visual perception
- balance and posture
- responses to sensory stimulation
- bilateral coordination
- motor planning

## **Management**

DCD is not curable but the child often improves in some areas with maturity. Liaison of education, health professionals and the child and parents is crucial to help the child within the classroom and the home environment. The school's special educational needs coordinator (SENCO) and school nurse can play an important role in the communication between health and education. Speech and language therapists and occupational therapists give advice to the school to help with difficulties in the classroom. Sometimes group and individual therapy can help, e.g. a phonology course for articulation difficulties. Advice for parents to help with home activities is also important.

## 7. ATTENTION DEFICIT HYPERACTIVITY DISORDER

It is estimated that up to 3% of school-age children meet the diagnostic criteria for attention deficit hyperactivity disorder (ADHD). It is more common in boys.

### Diagnosis

Problems occur in three areas:

- Inattention
- Hyperactivity
- Impulsiveness

It is possible to have one of these features without the others, e.g. marked inattention without the hyperactivity or hyperactivity without inattention.

In addition:

- The behaviour should have persisted for at least 6 months
- The behaviour should be inconsistent with the child's developmental age
- There must be clinically significant impairment in social or academic development
- The symptoms should occur in two or more settings including social, familial, educational and/or occupational settings
- There should be no other explanation for the symptoms, e.g. psychiatric illness

Diagnosis requires detailed history and information gathering from parents, school and other professionals. Structured questionnaires, e.g. Conner Scales, are used to screen and diagnosis ADHD.

Examination to exclude other differential diagnoses is important.

Children with ADHD develop emotional and social problems, poor school performance and problems within the home because of the difficult behaviour. It is associated with unemployment, substance abuse and crime in adulthood.

### Differential diagnosis

- Inappropriate expectations
- Language/communication disorder
- Social problem
- Specific learning difficulty
- Chronic illness, e.g. asthma
- Epilepsy
- DCD

- Drugs

## Management

Management involves a comprehensive treatment programme. There needs to be multiprofessional collaboration of the parents, the child, the school and other professionals. In some areas children with ADHD are managed by child psychiatrists and in others community paediatricians take on this role.

## Assessment

This should include assessment of:

- an individual's needs
- coexisting conditions
- physical health
- social, familial and educational/occupational circumstances

## Treatment

- **Psychological/behavioural interventions**; range of interventions from support groups through to psychotherapy can help including parent training/education programme (first line in pre-school age)
- **Educational support**: close communication with school is vital with the development of an individual education plan if necessary. Simple changes such as working in smaller groups, reward systems and moving the child nearer the teacher can help
- **Social services** – support if necessary
- **Drug treatment**; for older children and young people with severe ADHD, drug treatment should be offered as a first-line treatment but should always form part of a comprehensive treatment plan

Stimulant medications, e.g. methylphenidate (Ritalin), are used for the treatment of ADHD. They are usually given twice a day, morning and lunchtime. An evening dose is usually avoided because of difficulties with sleep. A drug holiday is recommended once a year. Side effects include weight and growth retardation and hypertension. Treatment should be started and monitored by child psychiatrists or paediatricians with expertise in ADHD. Height, weight, pulse and blood pressure should be monitored at least 6-monthly. Drug treatment does not cure ADHD. It improves the symptoms to allow the other interventions an opportunity to take effect.

- Methylphenidate can be used as part of a comprehensive treatment programme for children with severe ADHD as can atomoxetine and dexamfetamine
- Not licensed for those under 6 years
- Diagnosis should be made by a psychiatrist or paediatrician with expertise in ADHD
- The clinical expert should supervise the medication – GPs may agree to 'share care'
- Treatment should be stopped if there is no benefit
- Treatment should also include advice and support to parents and teachers

- Children should be regularly monitored
- Transition to adult care requires careful planning
- A balanced diet, good nutrition and regular exercise are recommended

## **8. SPECIAL EDUCATIONAL NEEDS AND THE EDUCATIONAL STATEMENT**

Many children have special educational needs, but only a small percentage (approximately 2%) need statements because their difficulties are such that they require provision additional to or different from that normally available to children.

- With the pre-school child it is often health that first becomes aware of the special educational needs, e.g. global developmental delay, Down syndrome, cerebral palsy
- Some medical conditions may have significant impact on the child's academic attainment and the ability to participate fully in the curriculum. Some of the most common medical conditions are congenital heart disease, epilepsy, cystic fibrosis, haemophilia and childhood cancers

### **Pre-school children**

- Health authorities are required by law to notify the local education authority (LEA) of children over the age of 2 years who may have special educational needs
- The parents, nursery and social services are also able to notify education
- The LEA then collects information about the child, which is passed on to the educational psychologist who decides if a formal assessment for statementing is appropriate
- If formal assessment is requested the health authority is asked to write a report on the child's needs – the 'E medical'. This report will give information about health, e.g. hearing, vision, epilepsy, physical problems, and a summary of the developmental problems. It also informs education of other therapists involved such as physiotherapy, and speech and language. In addition it describes the practical needs of the child, e.g. toileting, feeding, dressing, what to do if the child has a fit. Other professionals also submit reports including the parents

Once the formal assessment is completed the LEA decides whether to statement the child or not. (Most children are issued a statement after formal assessment.)

### **Schoolchildren**

When school or the family identify that a child has special educational needs, the school's SENCO should be informed. This is a teacher with expertise in managing children with educational needs. The school, with the help of the SENCO, will decide what support the child needs.

### **School Action**

A child is on 'School Action' if the school feels that they can support the child's needs with no additional support.

### **School Action Plus**

A child is on 'School Action Plus' if the school feels that help from other services is required, e.g. speech and language.

### **Educational Statement**

If the school feels that they can no longer support the child's educational needs sufficiently on School Action Plus, an assessment of educational needs is initiated. This formal assessment clarifies the child's needs, determines how these needs will be met within the educational setting, and decides whether a formal statement should be issued.

A statement is a legal contract and allows extra funding for the individual. When possible the child will continue in mainstream school with extra help, e.g. one-to-one full-time help.

Sometimes if it is felt more appropriate for the child to attend a special school with staff with expertise in special needs. These schools may be specific for one need, e.g. visual impairment, deafness or able to support children with multiple special needs.



---

## Child Mental Health

---

### 9. CHRONIC FATIGUE SYNDROME/MYALGIC ENCEPHALOPATHY

This remains an ill-understood condition that may present to either paediatricians or psychiatrists and which requires a coordinated multiprofessional approach. The cardinal symptoms are severe and disabling physical and mental fatigue lasting for more than 3 months. Symptoms are usually continuous, their effects on the individual manifest to a pathological degree and are rarely objectively confirmed. The diagnosis excludes known causes of chronic fatigue such as chronic illness and also excludes known psychological disease.

#### Aetiology

Although viruses such as Epstein–Barr virus and the enteroviruses are often implicated in the disease process, direct evidence of this is often hard to find. Case clustering does occur and, although anecdotal cases have suggested that immunization may be a trigger, there is no direct evidence to support this theory. The aetiology is likely to be a combination of physical, psychological and behavioural factors. Often a trigger for the child's symptoms can be found.

Depression may be an associated feature, and the chronic course the disease takes makes psychological support and evaluation essential.

#### Epidemiology

The UK prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in children and young people is 50–100 per 100 000 with the highest prevalence in adolescents. Where studies have reported a difference in gender, girls outnumber boys 3:1, but overall evidence of a gender difference is inconclusive.

#### Clinical features

The onset may be gradual or sudden. In addition to fatigue the following are other frequently reported symptoms:

- Headaches
- Sleep disturbance
- Concentration difficulties

- Memory impairment
- Myalgia/muscle pain
- Nausea
- Sore throat
- Tender lymph nodes
- Abdominal pain
- Arthralgia/joint pain
- Feeling too hot or too cold
- Dizziness
- Cough
- Eye pain
- Vision or hearing disturbance
- Weight gain or loss
- Muscle weakness
- Diarrhoea

There are no agreed diagnostic criteria for children/young people.

Some children and young people also have psychological symptoms, including depression/anxiety/social phobia/somatization/social withdrawal and typical personality features.

## **Initial assessment**

All patients referred for consideration of the diagnosis require a full and thorough assessment with an appreciation of the reality of the child's symptoms and acknowledgement of their validity. A thorough history and examination should be taken, exploring precise symptomatology. Organic and psychological disease should be looked for. Of particular importance is determining the effect of the child's symptoms on their normal daily routine including activities at home and attendance at school.

## **Investigation**

Routine tests on all patients should include a blood test and a urine test for the following investigations:

- Full blood count and film
- Erythrocyte sedimentation rate and C-reactive protein
- Blood glucose
- Blood biochemistry (to exclude renal insufficiency and Addison disease)
- Creatine kinase
- Thyroid function
- Liver function
- Urine for protein/glucose and infection screen
- Viral titres: Epstein–Barr virus IgM, IgG and EBNA (Epstein–Barr nuclear antigen)

Other investigations may be required if there are specific disease pointers.

Investigations should be performed early on and, if possible, on one occasion only to prevent reliance on test results. The differential diagnosis is wide and requires careful and comprehensive clinical assessment.

## Management

Management is complex and requires the input of many professionals. It needs to be tailor-made to the individual child in the form of a management plan with a single coordinator.

Key points are as follows:

- Facilitate the child and family to acknowledge the diagnosis, understand its implications and embark on a period of rehabilitation
- Assess current level of functioning by completing a daily programme to establish periods of eating, rest and activity
- Liaise closely with school/education authority
- Set goals:
  - Attendance at school is a key aim but gradual reintegration is usually required, with rest periods within school. Part days in school are preferable to exclusive home tuition
  - Aim to increase activity levels by around 5% each week
- Encourage child to keep a diary
- Advice re healthy balanced diet
- Help/support with sleeping difficulties
- Recognize early any predominant psychological symptoms, including school phobia or depression, and seek appropriate psychological or psychiatric help
- Appropriate pain management (may include psychological intervention and/or low-dose amitriptyline or nortriptyline)
- Pharmacological interventions such as corticosteroids, antidepressants (particularly selective serotonin re-uptake inhibitors – SSRIs) and immunoglobulin have been used, but in a recent meta-analysis of treatments only physiotherapy (with a graded exercise programme) was shown to have a clearly beneficial effect
- There is no evidence to support the use of magnesium injections, essential fatty acids, high-dose vitamin B<sub>12</sub> supplements, anticholinergic drugs, staphylococcal toxoid or antiviral therapies
- Cognitive techniques are used to assist patients to re-evaluate their understanding of the illness, combat depression and anxiety, and look for underlying thoughts and assumptions that may contribute to disability
- Inpatient admission is rarely needed in the context of children with severe/very severe CFS/ME
- It is critical to work closely with the child/young person and the family and to review progress regularly

---

See [here](#) for flow chart on the Management of Chronic Fatigue Syndrome

Patient < 18 years with:

- Debilitating fatigue not relieved by rest
- Other symptoms such as muscle pain, headache, sore throat; memory/sleep problems

Investigations:

- Thorough physical to include neurological exam; lymph node/liver/spleen/tonsillar enlargement; palpation over nasal sinus; lying and standing BP & HR
- General health and past medical history
- Assessment of psychological well being
- Family history of chronic illness
- Listen to patient, explore all symptoms/functional impairment

- Diagnose a generalised fatigue syndrome
- blood and urine tests for recommended investigations
  - FBC/film
  - ESR
  - CRP
  - iron studies
  - blood glucose
  - blood chemistry including CK, liver function, thyroid function, EBV, urinalysis
- Viral tests to exclude current infection are not recommended apart from EBV IgM, IgG and EBNA

Abnormal findings –  
probably not CFS/ME

Second line  
investigations for  
differential  
diagnosis

Abnormal

Normal

Not CFS/ME  
Treat/refer as  
appropriate

Likely CFS/ME  
but review  
results

Normal finding and  
debilitating fatigue persisting

- Diagnose CFS/ME: communicate reasons to family and document
- Reassess symptoms including psychological well being and functional impairment
- Agree management plan with family and other health professionals as appropriate and identify co-ordinator
- Inform school/LEA with consent if more than 15 days school missed or impairment will affect schooling
- Refer to psychology/psychiatry if significant morbidity and no local expertise or for specific behavioural interventions

Initiate management plan

- Establish baseline with activity diary
- When stable agree gradual increases in activity

Continued stable/  
improving baseline

Deterioration/no improvement  
after 6 mths or severe CFS/ME

Regular review to:

- Assess progress with management plan
- Assess how patient/family coping
- Identify any new or more severe symptoms
- Provide advice on diet + sleep
- Symptomatic treatment of pain, sleep problems and depression referring as necessary.

- Reassess management plan
- Consider specific behavioural interventions if patient well enough
- Consider referral to other health professionals
- Provide domiciliary visits if situation merits
- Only consider inpatient care for treatments not available on O/P basis

## Prognosis

Outcome data vary; studies with extended follow-up show 60–80% partial or complete. Younger people tend to have a better outcome.

Good prognostic factors in chronic fatigue syndrome are:

- Clearly defined trigger to illness
- Short duration of symptoms
- Supportive family with good interpersonal relationships
- Young age (adolescents overall do better than young or older adults)

## 10. EATING DISORDERS IN CHILDHOOD AND ADOLESCENCE

The eating disorders anorexia nervosa and bulimia nervosa have become increasingly recognized in paediatric practice over the last two decades. Both are rare in pre-pubertal children. Anorexia nervosa increases in incidence through mid- and late adolescence and is thought to affect at least 1% of females aged between 15 and 25 years. Bulimia nervosa most commonly presents in the late teens or early 20s. Over 90% of those affected by eating disorders are female.

Many clinical features are common to both anorexia and bulimia nervosa and patients may satisfy criteria for anorexia or bulimia at different stages of their illness.

### Diagnostic criteria for anorexia nervosa

- Self-induced weight loss of >15% body weight (avoidance of ‘fattening’ foods aggravated by self-induced vomiting, purging or exercise)
- Intense fear of gaining weight or becoming fat, even though underweight
- Abnormal perception of body image
- Amenorrhoea in postmenarchal female (absence of at least three menstrual cycles)

### Diagnostic criteria for bulimia nervosa

- Recurrent episodes of binge eating, characterized by consuming an excessive amount of food within a short, defined time span, with lack of control of eating during the episode
- Recurrent inappropriate compensatory behaviour to prevent weight gain, e.g. laxative abuse or self-induced vomiting
- Binges and compensatory behaviour occur at least twice per week for 3 months
- Self-evaluation unduly influenced by body shape and weight
- Disturbance does not occur exclusively during periods of anorexia nervosa

## Aetiology

- **Familial factors:** concordance rate for anorexia nervosa in monozygotic twins is 50%, compared with 10% for dizygotic twins. Other risk factors include family history of depression, alcoholism, obesity or eating disorder. Children with anorexia nervosa often come from overprotective and rigid families where there is a lack of conflict resolution
- **Individual factors,** e.g. previous obesity, fear of losing control, self-esteem dependent on the opinion of others and previous or ongoing abuse
- **Sociocultural factors:** there is a higher prevalence in high social classes and certain occupations, e.g. ballet dancers
- **Neurohumoral factors:** controversy remains over the exact role of substances such as serotonin in the pathogenesis of eating disorders

## Clinical features

### Anorexia nervosa

Usually this begins as a 'typical' adolescent diet to reduce stigmatization from obesity. Once weight begins to reduce, weight goals are constantly reset and compulsive weighing becomes a feature. Often physical activity is increased and social contacts diminish. Disordered thinking and poor concentration develop as the disease process progresses.

### Bulimia nervosa

Bulimia is even more common than anorexia in those with a past history of obesity. Self-loathing and disgust with the body are also greater than in anorexia. Patients are more likely to seek medical help for their symptoms. Coexisting substance abuse is not uncommon. Both bulimia and anorexia are frequently associated with major depressive and anxiety disorders.

## Medical complications of anorexia nervosa and bulimia

### Central nervous system

- Reversible cortical atrophy
- Non-specific EEG abnormalities

### Dental

- Caries
- Periodontitis

### Pulmonary

- Aspiration pneumonia (rare)

### Cardiovascular

- Bradycardia
- Hypotension
- Arrhythmias
- Cardiomyopathy (rare)

## **Gastrointestinal**

- Parotitis
- Delayed gastric emptying
- Gastric dilatation
- Constipation
- Raised amylase (bulimia)

## **Renal/electrolyte**

- Hypokalaemia
- Hypochloraemic metabolic alkalosis
- Oedema
- Renal calculi (rare)

## **Neuroendocrine**

- Amenorrhoea
- Oligomenorrhoea (bulimia)

## **Musculoskeletal**

- Myopathy
- Osteoporosis and pathological fractures

## **Haematological**

- Anaemia
- Thrombocytopenia
- Hypercholesterolaemia
- Hypercarotenaemia

## **Dermatological**

- Dry, cracking skin
- Lanugo
- Callous on dorsum of hand (from vomiting)
- Perioral dermatitis

## **Treatment**

Most patients with anorexia can be treated as outpatients, with hospital admission only if adequate weight gain at home is not possible or there are complications such as depression.

A combined multidisciplinary approach with monitoring of eating and weight, biochemical monitoring and ongoing psychotherapy is required. At present the psychotherapy usually involves behavioural, cognitive and psychodynamic components. Rarely, medication such as antipsychotics or antidepressants may be required. Appetite stimulants are used even less often. Adequate provision for

education is essential. Feeding against the will of the patient can be done only in the context of the Mental Health Act 1983 or the Children Act 1989.

Young people with bulimia may be treated with cognitive–behavioural therapy, adapted to suit their age and development. A trial of selective SSRIs may be considered but no other drugs are recommended for the treatment of bulimia nervosa.

## **Course and prognosis**

Five to ten years after the diagnosis of anorexia nervosa around 50% will have recovered, 25% will have improved but still have some features of an eating disorder and the remainder will either not have improved or be dead. Mortality rates are between 5% and 20%, with the most frequent causes of death being starvation, electrolyte imbalance, cardiac failure and suicide.

### **Good prognostic factors**

- Younger age at onset
- Less denial
- Improved self-esteem

### **Poor prognostic factors**

- Parental conflict
- Bulimia nervosa
- Coexisting behavioural disorders

The long-term outcome of bulimia nervosa is less clear.

## **11. DEPRESSION IN CHILDHOOD AND ADOLESCENCE**

Depression affects around 1 in every 200 children under the age of 12 years and 2–3 in every 100 teenagers. The cause is usually multifactorial but recognized ‘risk factors’ include the following:

- Adverse personal experiences/life events such as family breakdown, death of friend/family member, neglect, abuse, bullying
- Physical illness including infectious mononucleosis (acute trigger) or chronic disease
- Stress – especially if unable to share concerns and/or lack of practical support
- Positive family history
- Female sex
- History of drug/alcohol problems

## **Symptoms**

These include the following:



- Moodiness/irritability
- Withdrawal from friends, family, regular activities
- Self-critical/self-blaming
- Poor concentration
- Lack of care for personal appearance
- Changes in sleep pattern – may sleep too little or too much
- Tiredness
- Changes in appetite
- Frequent minor health problems particularly headaches/abdominal pain

## **Treatment**

General advice should be given to all children and young people with mild, moderate or severe depression on:

- self-help materials
- the benefits of regular exercise
- sleep, hygiene and anxiety management
- the benefits of a balanced diet

Mild depression: if this persists for 4 weeks or more with no significant comorbid problems or suicidal ideation, offer one of the following psychological therapies for a limited period of 2–3 months:

- Individual non-directive supportive therapy
- Group cognitive–behavioural therapy
- Guided self-help
- Antidepressant medication should not be used for the initial treatment of mild depression

Moderate/severe depression:

- First-line treatment is psychological therapy such as individual cognitive–behavioural therapy or interpersonal therapy or family therapy
- If depression is unresponsive consider additional psychological therapies or medication (after multidisciplinary review)
- Fluoxetine is the most commonly prescribed but it is not licensed for under-18s and should be used extremely cautiously, especially in under-11s
- Second-line drug treatments include sertraline and citalopram

High-risk of suicide, serious harm and self-neglect:

- Consider inpatient treatment
- Use electroconvulsive therapy very rarely in 12–18 year olds

Do not use:

- Paroxetine, venlafaxine, tricyclic antidepressants, St John's wort

Consideration should be paid to the parent's mental health particularly the possibility of depression and substance abuse.

## 12. SELF-HARM AND SUICIDE

Suicide is rare before puberty, yet it is the third leading cause of death for adolescents with rates in young men continuing to rise. Methods include drug overdose, hanging, inhalation of car exhaust fumes and shooting. It is by far the minority of adolescents making suicide attempts who have either an underlying psychiatric disorder or serious suicidal intent. All individuals who attempt suicide must undergo psychiatric assessment. The use of violent methods, attempts that take place in isolated places and the writing of a suicide note should ring particular alarm bells.

### Risk factors for suicide in adolescents

- Male sex
- Broken home, disturbed relationships with parents
- Living alone
- Immigrant status
- Family history of affective disorder, suicide or alcohol abuse
- Recent loss or stress
- Previous suicide attempt
- Drug or alcohol addiction

### Characteristics of deliberate self-harm in adolescents

#### Self-poisoning

- Much more common in girls
- Accounts for >90% of cases of deliberate self-harm
- Overdose often taken in environment where patient is likely to be found
- Drugs most commonly taken include paracetamol, aspirin, benzodiazepines and antidepressants
- Multiple drug ingestion common (often with alcohol)
- Under 20% need intensive medical management but all should be admitted until assessed by child psychiatrist/social services as appropriate
- Mortality rate well below 1%
- Blood and urine toxicology screens are useful because there is often a poor correlation between the quantity of drugs taken and their clinical effect
- Paracetamol and aspirin levels should be taken routinely

#### Self-mutilation

- Includes scratching, cutting, cigarette burns, tattooing, bruising, biting and inserting needles

- Typically seen in teenage girls with personality problems, e.g. aggressive/impulsive behaviour, eating disorders, poor self-esteem
- Also occurs in those with schizophrenia/learning disability

Difficult to treat – need to address underlying personality/emotional problems.

Over 10% of adolescents who attempt suicide will repeat within 1 year.

## 13. SCHIZOPHRENIA WITH CHILDHOOD ONSET

Schizophrenia is rare in childhood and adolescence with an incidence of less than 3 in 10 000. A genetic component can be implicated in at least 10% of cases, but other factors, including perinatal difficulties, psychosocial factors and difficulties with premorbid personality, are also important. Boys outnumber girls by approximately 2:1.

### Presentation

May be acute or insidious (gradual withdrawal and failing schoolwork).

Major symptoms include:

- Delusions
- Hallucinations
- Distortions of thinking (thought insertion and withdrawal)
- Movement disorders, commonly catatonia

### Differential diagnosis

It may be difficult to distinguish from major mood disturbance, e.g. manic–depressive psychosis, or organic causes of psychosis, e.g. neurodegenerative or drug-induced episode, systemic lupus erythematosus, epilepsy, Wilson disease, thyrotoxicosis and vasculitis. Any child presenting with psychotic symptoms should have an EEG and brain MRI.

### Treatment

- Drugs: antipsychotics, e.g. clozapine (few extrapyramidal side effects but risk of agranulocytosis), chlorpromazine, haloperidol
- Individual and family therapy
- Adequate educational provision essential

### Prognosis

- Chronic or relapsing course is common

- Good prognostic factors include high intelligence, acute onset, precipitating factors, older age at onset and normal premorbid personality

## 14. CONDUCT DISORDERS

Persistent antisocial or socially disapproved of behaviour often involving damage to property and unresponsive to normal sanctions.

### Prevalence

- Approximately 4%
- Strong male predominance

### Clinical features

- Temper tantrums
- Oppositional behaviour (defiance of authority, fighting)
- Overactivity
- Irritability
- Aggression
- Stealing
- Lying
- Truancy
- Bullying
- Delinquency, e.g. stealing, vandalism, arson in older children/teenagers

‘Oppositional defiant disorder’ is a type of conduct disorder characteristically seen in children under 10 years. It is characterized by markedly defiant, disobedient, provocative behaviour and by the absence of more severe dissocial or aggressive acts that violate the law or the rights of others.

### Aetiology

- Family factors: lack of affection, marital disharmony, poor discipline, parental violence/aggression
- Constitutional factors: low IQ, learning difficulties, adverse temperamental features
- Oppositional peer group values
- Urban deprivation/poor schooling
- Depression
- Bullying
- Abuse

### Differential diagnosis

Young people with conduct disorders have an increased incidence of neurological signs and

symptoms, psychomotor seizures, psychotic symptoms, mood disorders, ADHD and learning difficulties.

## **Treatment**

- Family/behavioural therapy
- Practical social support, e.g. rehousing

## **Prognosis**

- Half have problems into adult life

# **15. COMMON BEHAVIOURAL PROBLEMS IN PRE-SCHOOL CHILDREN**

## **15.1 Sleep disorders**

Reluctance to settle at night and persistent waking during the night are common problems in young children, with one in five 2 year olds waking at least five times per week.

### **Factors contributing to sleep difficulties**

- Adverse temperamental characteristics in child
- Perinatal problems
- Maternal anxiety
- Poor accommodation
- Physical illness
- Medication, e.g. theophyllines
- Timing of feeds
- Co-sleeping with parents

Medication, such as sedating antihistamines, is usually unhelpful in this situation. A behavioural strategy is usually successful but often needs to be combined with some respite for the parents. Unlicensed melatonin is, however, sometimes used to reduce both the time to sleep onset and the number of episodes of night waking. Its use in children with coexisting neurodevelopmental pathology has been well described.

Nightmares are most common between the ages of 3 and 5 years with an incidence of between 25% and 50%. The child who awakens during them is usually alert and can recall the dream and frightening images. They are usually self-limiting and may be related to obvious frightening or stressful events. In severe cases the involvement of a psychologist or psychiatrist may be needed.

## **15.2 Feeding problems in infancy and childhood**

Most children at some point will be ‘picky eaters’ – a phase that will usually pass spontaneously. Infants and children may also, however, refuse to feed if they find the experience painful or frightening. Reasons contributing to this may include the following:

- Unpleasant physical experiences associated with eating, e.g. gastro-oesophageal reflux, oral candidiasis, stricture postoesophageal atresia repair
- Oral motor dysfunction
- Children who have required early nasogastric tube feeds
- Maternal depression
- Being forced to eat by caregiver
- Developmental conflict with caregiver
- Emotional and social deprivation

Non-organic faltering growth is a diagnosis of exclusion.

## **Evaluation of feeding disorders**

- Complete history including detailed social history
- Complete physical examination – need to exclude physiological, anatomical and neurological abnormalities
- Assess emotional state and developmental level
- Observe feeding interaction
- Help parents to understand that infants and children may have different styles of eating and food preferences

## **Management of feeding disorders**

- Eliminate and/or treat physical cause
- Multidisciplinary approach including paediatrician, GP, health visitor, speech and language therapist, dietician and/or psychologist
- Child’s behaviour may need modification
- If there is also faltering growth, exclude medical disorders and maltreatment

**Pica** (the ingestion of inedible material such as dirt and rubbish) may be normal in toddlers but persistent ingestion is found in children with learning difficulties and in psychotic and socially deprived children. Lead poisoning is a theoretical risk from pica.

## **15.3 Temper tantrums**

These are common in the pre-school child and generally occur when the child is angry or has hurt him- or herself. Usually they are typified by screaming and/or crying, often in association with collapsing to the floor. It is rare for children to injure themselves during such episodes. If necessary the child should be restrained from behind by folding one’s arms around the child’s body. It is

important to minimize any additional attention to the child and to respond and praise only when behaviour is back to normal.

## 15.4 Breath-holding attacks

These episodes typically occur after a frustrating or painful experience. The child cries inconsolably, holds his or her breath and then becomes pale or cyanosed. In the most serious cases loss of consciousness may ensue and there may be stiffening of the limbs or brief clonic movements. Clearly it may be difficult to distinguish from a generalized seizure; however, the fact that after a breath-holding attack the child will take a deep breath and immediately regain consciousness may facilitate differentiation. Typical onset is between 6 and 18 months. No specific treatment is needed and the episodes diminish with age.

## 16. COMMON PROBLEMS IN THE SCHOOL-AGED CHILD

### 16.1 School refusal

This problem refers to the child's irrational fear about school attendance and is seen most commonly at the beginning of schooling or in association with a change of school or move to secondary school. Typically the child is reluctant to leave home in the morning and may develop a headache or abdominal pain.

#### **Factors contributing to school refusal**

- Separation anxiety
- Specific phobia about an aspect of school attendance, e.g. travelling to school, mixing with other children, games lessons
- A more generalized psychiatric disturbance such as depression or low self-esteem
- Bullying

#### **Characteristics of school refusers**

- Good academic achievements
- Conformist at school
- Oppositional at home

#### **Treatment**

- Avoid unnecessary investigation of minor somatic symptoms
- Early, if necessary graded, return to school
- Support for parents and child
- Close liaison with school

In chronic cases a gradual reintegration back into school is required, possibly with a concurrent specific behavioural programme and targeted family therapy.

Overall two-thirds of children will return to school regularly. Those who do badly are often adolescents from disturbed family backgrounds.

## **Truancy**

In contrast to the above, truancy always reflects a lack of desire to go to school rather than anxiety re school attendance and as such may be part of a conduct disorder.

## **Bullying**

Bullying may be defined as ‘the intentional unprovoked abuse of power by one or more children to inflict pain or cause distress to another child on repeated occasions’. Estimates on the prevalence of bullying vary widely, but many studies report that between 20% and 50% of school-aged children have either participated in or been victims of bullying. Verbal harassment is the most common form of bullying and is often not recognized as such. ‘Cyber’ bullying is increasing in prevalence, particularly among older children.

Although it is important not to stereotype, certain characteristics are commonly exhibited by bullies:

- Poor psychosocial functioning
- Unhappiness in school
- Concurrent conduct disorders
- Emotional problems
- Social problems
- Alcohol and nicotine abuse

Children who suffer at the hands of bullies may consequently suffer from:

- anxiety
- insecurity
- low self-esteem and self-worth
- mental health problems
- sleep difficulties
- bed wetting
- headaches
- abdominal pain

Carefully planned programmes may reduce the incidence of bullying by 50% or more. Such strategies rely on teaching appropriate social skills to children who bully, developing clear rules that they are expected to adhere to, providing an increased level of supervision, particularly within the school environment, and facilitating access to other services that they may require, e.g. child mental health,



social services.

## 16.2 Non-organic abdominal pain/headache/limb pains

Over 10% of children experience such symptoms. It is important to exclude organic pathology promptly and to search for any underlying stresses. Most run a short course but if symptoms are persistent and involve several systems the term ‘somatization disorder’ is used.

## 16.3 Sleep problems in the school-aged child

To understand sleep disorders a basic knowledge of the sleep cycle is necessary.

### Sleep stages

Sleep consists of several stages that cycle throughout the night. One complete cycle lasts 90–100 minutes.

### Stages of Sleep

Sleep stage	Features
	Transition state between sleep and wakefulness Eyes begin to roll slightly
1 Slow wave sleep (SWS) or non-rapid eye movement (NREM)	Mostly high-amplitude, low-frequency theta waves Brief periods of alpha waves — similar to those when awake Lasts only a few minutes
2 SWS or NREM	Peak of brain waves higher and higher sleep spindles Lasts only few minutes
3 SWS or NREM	Also called delta sleep or deep sleep Very slow delta waves account for 20–50% of brain waves
4 SWS or NREM	Also called delta sleep or deep sleep Over 50% of brain waves are delta waves Last and deepest of sleep stages before REM sleep
5 REM	Frequent bursts of rapid eye movement and occasional muscular twitches Heart rate increases

Rapid shallow respirations

Most vivid dreaming during this phase

## **Night terrors**

These are most commonly seen in children between the ages of 4 and 7 years. Typically the child wakes from deep or stage 4 sleep apparently terrified, hallucinating and unresponsive to those around him or her. Usually such episodes last less than 15 minutes and the child goes back to sleep, with no recollection of the events in the morning. It is unusual to find any underlying reason or stresses contributing to the problem.

## **Nightmares**

These occur during rapid eye movement (REM) sleep and the child remembers the dream either immediately or in the morning. Underlying anxieties should be sought.

## **Sleepwalking**

This occurs during stages 3 or 4 of sleep and is most often seen in those between 8 and 14 years.

## **16.4 Tics**

These occur transiently in 10% of children and are much more commonly seen in boys. Onset is usually around the age of 7 years, although simple tics are seen most commonly. Gilles de la Tourette syndrome may occur in childhood. This phenomenon is characterized by complex tics occurring in association with coprolalia (obscene words and swearing) and echolalia (repetition of sounds or words).

## **Factors predisposing to tics**

- Positive family history
- Stress (including parental)
- Neurodevelopmental delay

## **Treatment**

- Most resolve spontaneously
- Reassure accordingly
- Behavioural or family therapy if appropriate
- Medication: haloperidol, pimozide, clonidine (in very severe cases only)

## **Outcome**

- Simple tics – complete remission
- Gilles de la Tourette syndrome – 50% have symptoms into adult life

## 17. ENURESIS/ENCOPRESIS

### 17.1 Enuresis

This is defined as the involuntary passage of urine in the absence of physical abnormality after the age of 5 years. Nocturnal enuresis is much more common than diurnal enuresis, affecting at least 10% of 5 year olds. Although most children with nocturnal enuresis are not psychiatrically ill, up to 25% may have signs of psychiatric disturbance. Diurnal enuresis is much more common among girls and those who are psychiatrically disturbed. Secondary enuresis is more commonly associated with underlying problems.

#### Aetiology

- Positive family history in 70%
- Developmental delay
- Psychiatric disturbance
- Small bladder capacity
- Recent stressful life events
- Large family size
- Social disadvantage

#### Treatment

- Exclude physical basis (history, examination, urine culture  $\pm$  imaging)
- Look for underlying stresses
- Reassure child and parents of benign course
- Star chart
- Enuresis alarm (7 years and older)
- Drugs (short-term control only): desmopressin, tricyclic antidepressants

It must be remembered that child sexual abuse may present with enuresis and/or encopresis.

### 17.2 Encopresis

This is defined as the inappropriate passage of formed faeces, usually on to the underwear, after the age of 4 years. It is uncommon, with a prevalence of 1.8% among 8-year-old boys and 0.7% for girls. Psychiatric disturbance is common and enuresis often coexists. Broadly speaking, children with encopresis may be divided into those who retain faeces and develop subsequent overflow

incontinence (retentive encopresis) and those who deposit faeces inappropriately on a regular basis (non-retentive).

## **Type of encopresis and common family characteristics**

- Retentive – obsessional toilet-training practices
- Non-retentive – continuous, disorganized, chaotic families

## **Other risk factors for encopresis**

- Poor parent–child relationship
- Emotional stresses (including sexual abuse)
- Past history of constipation/anal fissure

## **Treatment**

- Exclude physical problems, e.g. Hirschsprung disease/hypothyroidism/hypercalcaemia
- Laxatives to clear bowel
- Education for parents and child
- Star chart
- Individual psychotherapy
- Family therapy

It is unusual for this problem to persist into adolescence.

---

# Community Paediatrics

---

## 18. CHILD HEALTH SURVEILLANCE

This begins in the antenatal period with a major focus on antenatal care, support for both parents and early identification of 'at-risk' families. Health promotion and advice on feeding are shared.

Although all children are assigned a health visitor, increasingly their input is targeted and varied. All infants have a parent-held child health record 'red book' and in this all contacts with health professionals should be documented. The most appropriate opportunities for screening tests and developmental surveillance, as well as for discussing social and emotional development with parents and children and linking children to early years services, are as follows:

- Week 12 of pregnancy
- Neonatal examination: performed by nurse practitioner, hospital doctor or GP. Full physical examination including weight, head circumference, heart, eyes, hips, genitalia.
- New baby review – at 14 days when health visitor takes over from community midwife
- 6- to 8-week check – usually done by GP and often combined with first immunisations.
- 1-year checks – performed variably in different geographical areas
- 2 1/2-year checks – performed variably in different geographical areas

### 18.1 Summary of newborn screening

1. Newborn hearing screening offered to all babies in the UK by 4–5 weeks of age uses combination of automated otoacoustic emissions (AOAEs) and automated brain-stem response (AABR) should be done by 44 weeks' gestational age
2. Phenylketonuria screening (PKU)
3. Congenital hypothyroidism
4. Sickle cell disease and thalassaemia
5. Cystic fibrosis
6. Medium chain acyl-CoA dehydrogenase deficiency (MCADD)

The last five tests are all performed on a heel-prick sample taken from all neonates by a midwife or health visitor at age 5–8 days.

## 18.2 School-aged children

Programmes differ significantly between local authorities. A health questionnaire is completed on school entry and reviewed by the school nurse. Screening of hearing and vision may also be undertaken. In most areas medical examination is carried out only on a selective basis.

Informal ‘drop-in centres’ run by the school nurse provide valuable support to the child and their family. A full medical may be requested if parents, teachers or school nurse have concerns.

## 19. IMMUNIZATION IN CHILDHOOD

### 19.1 Immunization schedule

**The current immunization schedule for infants and children in the UK (active from November 2010)**

When to immunize	Diseases protected against	Vaccine given	Immunization site
Two months old	Diphtheria, tetanus, pertussis, polio and <i>Haemophilus influenzae</i> type b (Hib)	DTaP/IPV/Hib (Pediace)l	Thigh
	Pneumococcal disease	PCV (Prevenar 13)	Thigh
Three months old	Diphtheria, tetanus, pertussis, polio and Hib	DTaP/IPV/Hib (Pediace)l	Thigh
	Meningococcal group C disease (MenC)	MenC (Menjugate or Neisvac C)	Thigh
Four months old	Diphtheria, tetanus, pertussis, polio and Hib	DTaP/IPV/Hib (Pediace)l	Thigh
	MenC	MenC (Menjugate or Neisvac C)	Thigh
	Pneumococcal disease	PCV (Prevenar 13)	Thigh
Between 12 and 13 months old – within a month of the first birthday	Hib/MenC	Hib/MenC (Menitorix)	Upper arm/thigh
	Pneumococcal disease	PCV (Prevenar 13)	Upper arm/thigh
	Measles, mumps and rubella	MMR (Priorix or MMR VaxPRO)	Upper arm/thigh
Three years four months old or soon after	Diphtheria, tetanus, pertussis and polio	DTaP/IPV (Repevax) or DTaP/IPV (Infanrix-IPV)	Upper arm
	Measles, mumps and rubella	MMR (Priorix or MMR VaxPRO) (check first dose has been given)	Upper arm
Girls aged 12 to 13 years old	Cervical cancer caused by human papillomavirus types 16 and 18	Cervarix	Upper arm
Thirteen to 18 years old	Tetanus, diphtheria and polio	Td/IPV (Revaxis), and check MMR status	Upper arm

### Notes on immunization schedule

## **Bacille Calmette–Guérin (BCG) vaccine**

High-risk categories include:

- Infants born to immigrants from countries with high prevalence of tuberculosis
- Infants who are to travel abroad to high-prevalence areas
- Infants born in the UK where high prevalence of tuberculosis

## **Rubella vaccine**

Any girl who missed the MMR should be immunized between the ages of 10 and 14 years.

## **Hepatitis B vaccine**

At present the vaccine is recommended only for:

- babies born to mothers who are chronic carriers of hepatitis B virus or to mothers who have had acute hepatitis B during pregnancy
- families adopting children from countries such as south-east Asia, in whom hepatitis status is unknown

## **19.2 Contraindications to immunization**

### **General considerations**

- **Acute illness:** immunization should be deferred if the individual is acutely unwell but not if he or she has a minor infection without fever or systemic upset
- **Previous severe local or general reaction:** if there is a definite history of severe local or general reaction to a preceding dose, then subsequent immunization with that particular vaccine should not be performed
- **Local reactions:** extensive redness and swelling which becomes indurated and involves most of the anterolateral surface of the thigh or a major part of the circumference of the upper arm
- **General reactions:** this is defined as: fever  $>39.5^{\circ}\text{C}$  within 48 hours of immunization; anaphylaxis; bronchospasm; laryngeal oedema; generalized collapse. In addition, prolonged unresponsiveness; prolonged inconsolable or high-pitched screaming for more than 4 hours; convulsions or encephalopathy within 72 hours

### **Live vaccines (e.g. BCG, MMR)**

Contraindications to live vaccine administration include the following:

- Prednisolone (orally or rectally) at a daily dose of 2 mg/kg per day for at least a week or 1 mg/kg per day for a month; corticosteroid use via other routes (e.g. intra-articular or inhaled) does not contraindicate live vaccine administration
- Children on lower doses of steroid also on cytotoxic drugs or with immunosuppression secondary to an underlying disease process

- Those with impaired cell-mediated immunity, e.g. DiGeorge syndrome
- Children being treated for malignant disease with chemotherapy and/or radiotherapy, or those who have completed such treatment within the last 6 months
- Children who have received a bone marrow transplant within 6 months
- Immunoglobulin administration within previous 3 months

## Specific contraindications

- Egg allergy – individuals with confirmed anaphylactic reaction to egg should not receive influenza or yellow fever vaccines. MMR can be safely given to most children who have had allergic reactions to egg. For those with confirmed anaphylactic reaction many can be immunized under controlled conditions
- Severe latex allergy – vaccines should be given from latex-free syringes/vials
- Pregnancy – delay live vaccines until after delivery

## Myths surrounding contraindications

The following are **NOT** contraindications to immunization:

- Family history of adverse immunization reaction
- Stable neurological condition, e.g. Down syndrome or cerebral palsy
- Egg allergy – hypersensitivity to egg contraindicates influenza vaccine and yellow fever vaccine, but there is good evidence that MMR can be safely given to children who have had previous anaphylaxis after egg
- Personal or family history of inflammatory bowel disease does not contraindicate MMR immunization
- Family history of convulsions
- Mother is pregnant

In addition, it should be noted that the Council of the Faculty of Homeopathy strongly supports the immunization programme.

## 19.3 Immunization reactions

These can be localized or generalized. Predictable adverse reactions (side effects) are generally mild and resolve quickly. They are known as adverse events following immunization (AEFIs). AEFIs may be due to inappropriate practices in the provision of immunization, e.g. wrong dose/prepared incorrectly. These are known as programme-related AEFIs.

In contrast vaccine-induced AEFIs are reactions in individuals specifically caused by a particular vaccine or its component parts. These may be induced, direct effects of the vaccine or one of its components and/or due to an underlying medical condition or an idiosyncratic response in the recipient.



# Examples of vaccine-induced AEFIs

- Direct effects:
  - Local reactions and fever within 48 hours of DTaP/IPV/HiB
  - Rash and fever 7–10 days after MMR
  - Parotitis after MMR
- AEFIs due to underlying medical condition – vaccine-associated paralysis after use of live attenuated oral polio vaccine in child with previously unrecognized severe combined immune deficiency
- Idiosyncratic responses – idiopathic thrombocytopenic purpura (ITP) within 30 days of MMR and anaphylaxis after immunization

## Coincidental AEFIs

These are not true adverse reactions to immunizations or vaccines but linked only because of the timing of their occurrence, e.g. development of a cold after a flu immunization.

## Common vaccine-induced AEFIs

- Pain, swelling or redness at site of injection
- Local adverse reactions that start within a few hours and are usually mild or self-limiting. Although often referred to as hypersensitivity reactions, they are not allergic in nature but may be due to high titres of antibody or a direct effect of the vaccine product. These do not contraindicate further doses
- Systemic side effects: these include fever, myalgia, malaise, irritability and loss of appetite.

## 19.4 Additional information on vaccines

Vaccine type		Other specific contraindications <sup>a</sup>	Side effects <sup>b</sup>	Comments
Diphtheria	Inactivated toxoid + adjuvant (given as part of combined immunization)	As above	Swelling + redness common Malaise, fever, headache Severe anaphylaxis rare Neurological reactions very rare	
Tetanus	Inactivated toxoid+ adjuvant (given as part of combined immunization)	As above Previous anaphylactic reaction or allergy to neomycin, streptomycin, polymyxin B	Pain, redness, swelling common General reactions uncommon Malaise, myalgia, pyrexia Acute anaphylaxis and urticaria are common Peripheral neuropathy rare	
Pertussis	Killed <i>Bordetella pertussis</i> (as part of DTP) Acellular pertussis now used	As above + evolving neurological problem Previous anaphylactic reaction to pertussis vaccine or neomycin streptomycin or polymyxin B	Swelling and redness at injection site less common with acellular vaccine Crying, fever Persistent screaming and collapse now rare with current vaccines Convulsions and encephalopathy very very rare and link with vaccine itself contentious Much more common after disease than immunization	

Polio	Enhanced potency inactivated polio vaccine (IPV) (given as part of combined immunization)	Contraindications Inactivated polio vaccine (IPV) Acute or febrile illness Extreme polymyxin B and neomycin sensitivity	Pain, redness, swelling, fever, convulsion, screaming, pallor, limpness (rare), anaphylaxis (very rare)	
Hib	Conjugate (given as part of combined immunization)	As above	Local swelling and redness Fever, convulsions, screaming, pallor and limpness, anaphylaxis (very rare)	Disease incidence has fallen dramatically since introduction in 1992
MMR	Live, attenuated	As above + allergy to neomycin or kanamycin	Malaise, fever, rash within 7–10 days. Parotid swelling 1% Febrile convulsion 1/1000 Arthropathy/thrombocytopenia rare Theoretical risk of encephalitis but causal evidence lacking Encephalitis much more likely secondary to measles in unimmunized child All side effects less common after second dose	Medical Research Council and CSM concluded no link between MMR and autism or bowel disease Separate vaccines may be harmful. Adverse publicity led to a fall in uptake rates and consequent increased risk of measles outbreak
Men C	Conjugate (carrier proteins are diphtheria toxoid or tetanus toxoid derivatives)	As above + hypersensitivity to vaccine components including diphtheria toxoid or tetanus toxoid	Swelling at injection site common particularly in older children Systemic symptoms including irritability and fever much more common in infants, as is impaired sleep Headaches, dizziness, myalgia and drowsiness	Protects against <i>N. meningitidis</i> group C only If travelling abroad, should still receive meningococcal polysaccharide
BCG	Live, attenuated A and C vaccines	As above + positive sensitivity skin test to tuberculin protein Generalized septic skin conditions	Vertigo and dizziness occasional Immediate allergy/anaphylaxis rare Severe injection site problems usually due to poor injection technique Adenitis Lupoid-type local reaction (rare) Widespread dissemination of organism (very rare)	If child has eczema give at eczema-free site Tuberculin skin test must be done First in all children over 3 months Reaction to tuberculin protein may be suppressed by: infectious mononucleosis, other viral infection, live viral vaccines, Hodgkin's disease, sarcoid, corticosteroids, immunosuppressant treatment or diseases

## 20. ADOPTION AND FOSTERING

### 20.1 Adoption

Adoption is about meeting the needs of a child and not those of the prospective parents. When a child is adopted full parental rights are taken on by the adopting parents and the child has all the rights of a natural child of those parents. Up to 4000 children per year are adopted in the UK, most of these being children over 4 years of age. Over half involve children being adopted by step-parents. Adoption of newborn babies is increasingly uncommon. Although infants and children from overseas are brought into the UK for adoption, it must be recognized that the legal complexities surrounding this area are immense.

In England and Wales social services and voluntary organizations act as adoption agencies. Before any child is adopted the following steps must occur:

- Freeing of child for adoption – baby/child's natural parents must give consent for adoption. Cannot be done until at least 6 weeks after birth for newborn infants. May not be required if parents are deemed incapable of decision-making (e.g. severe mental illness)
- Meticulous assessment of prospective adoptive parents – carried out by social services. There are

very few absolute contraindications to adoption (certain criminal offences will exclude). Detailed medical history of prospective parents is important to ensure that they are physically able to look after child. Disabled adults are encouraged to adopt. Choice of family will ideally reflect birth heritage of child (i.e. ethnic origin)

- Application for adoption order – can be applied for as soon as the child starts living with prospective adoptive parents but it will not be heard for at least 3 months (for newborn infants the 3-month period begins at the age of 6 weeks)
- Adoption hearing – an Adoption Panel, including social workers and medical advisers, consider the needs of both the child and the prospective parents. May be contested. Decision on day as to whether Adoption Order to be granted

Medical services are involved at two levels:

- In an advisory capacity to the adoption agency, e.g. scrutinizing reports, collecting further medical information if needed
- Carrying out pre-adoption medicals – it is essential that prospective parents have all available information on, for example, the health of both natural parents, pregnancy, delivery, neonatal problems, development, etc. so that they can make a fully informed decision about adopting the child. Any special needs of the child should be identified at such an examination and additional reports by psychiatrists/psychologists may be needed. Children with special needs usually thrive in secure family environments, but full medical information must be made available to prospective adopters.

There are no medical conditions in the child that absolutely contraindicate adoption.

## 20.2 Fostering

Foster care offers a child care in a family setting but does not provide legal permanency because parental rights remain with the natural parents, local authority or courts, depending on the legal circumstances. Different types of foster care include the following:

- Care of babies awaiting adoption
- Young children in whom return to parents is anticipated
- Short break fostering
- Remand fostering

For some children with strong natural family ties long-term fostering is appropriate.

Foster parents are selected by a foster panel and, as with adoption, their health and that of the children awaiting fostering is considered.

Foster carers receive a financial allowance.

# 21. THE CHILDREN ACT 1989 AND HUMAN RIGHTS ACT 1998

## 21.1 Aims of the Children Act

This Act introduced extensive changes to legislation affecting the welfare of children. Its main aims included:

- restructuring custody and access in divorce
- moving towards a 'family court' handling all public and private proceedings about children
- creating a single statutory code for the protection of children through the courts
- promoting interagency cooperation in the prevention, detection and treatment of child abuse and neglect
- making legal remedies more accessible while also encouraging negotiation, partnership and agreed solutions that avoid the need to resort to court

In all of the above, the Act stresses that the child's welfare is the paramount consideration. It provides a checklist of welfare parameters aimed at ensuring that, in planning for the child's protection and upbringing, full account is taken of his or her needs, wishes and characteristics.

### Child protection issues contained in the Act

Social services have a duty to investigate if they have reasonable cause to suspect that a child has suffered, is suffering or is likely to suffer 'significant harm'. If investigation confirms the suspicion then the child may need to be accommodated by social services while matters are taken further. Parents of an accommodated child retain full parental responsibility, including the right to remove the child at any time. An Emergency Protection Order may be available, enabling the child to be detained in hospital, if parents do not agree to voluntary admission.

### Emergency Protection Order

This replaced the 'Place of Safety Order' and may be needed if, for example, non-accidental injury is suspected. The order lasts a maximum of 8 days with a possibility of extension for a further 7 days. It may be granted by the court if one of the following is satisfied:

- There is reasonable cause to believe that the child is likely to suffer appreciable harm if not removed from his or her current accommodation
- Enquiries by local authority or an 'authorized person' are being frustrated by lack of access

In addition, a child likely to suffer significant harm may also be taken into **police protection** for 72 hours. This involves a decision internal to the police force, and in cases of extreme emergency is likely to be quicker than applying for an Emergency Protection Order.

### A Care Order

This order confers parental responsibility on the social services (in addition to that of the parents) and usually involves removal from home, at least temporarily. It may be applied for in cases of non-accidental injury, where enquiries will take some time and where the child is not regarded as being 'safe' at home.

## **A Supervision Order**

This gives social services the power and duty to visit the family and also to impose conditions, such as attendance at clinic, nursery, school or outpatient visits.

Both care and supervision orders may be taken out by a court if that court is convinced that thresholds for appreciable harm to the child have been met. The court, however, is under duties to consider the full range of its power and not to make any order unless doing so would be better for the child than making no order. While proceedings for either of these orders are pending, the court may make 8- and then 4-weekly cycles to allow time for the child's needs to be comprehensively assessed, and for parties to prepare their proposals for court.

## **Child Assessment Order (CAO)**

This order may be used if there is a situation of persistent but non-urgent suspicion of risk. It is available if:

- significant harm is suspected
- a necessary medical or other assessment would be unlikely or unsatisfactory without a court order

It therefore overrides the objections of a parent to whatever examination or assessment is needed to see whether the significant harm test is satisfied. In addition it may override the objection of a child who 'is of sufficient understanding to make an informed decision'. This order lasts up to 7 days.

## **Wardship**

If insufficient powers are available via the Children Act then wardship via the High Court may be applied for. This gives the court almost limitless powers and is used in exceptional circumstances, such as when a family objects to surgery or medical treatment for religious reasons.

Despite all the above, the implementation of the Children Act has been associated with a significant reduction in the number of compulsory child protection interventions through the courts, in part because of greater social services' reliance on voluntary help and increased partnership with parents.

## **21.2 Human Rights Act 1998**

This Act requires that all UK law be interpreted in accordance with the European Convention of Human Rights so as to give effect to the requirements of the convention rights. The Act enables

individuals to take action for breach of these rights which include:

- Article 2 – Right to life
- Article 3 – Prohibition of torture
- Article 6 – Right to a fair trial
- Article 8 – Right to respect for private and family life

During child protection investigations there is potential conflict between the right of the child's family (Article 8) and the duties of the child protection team as they relate to Articles 2 and 3. Legal advice will need to be sought in situations of doubt.

## **22. SUDDEN INFANT DEATH SYNDROME AND CHILD DEATH REVIEW**

### **Definition**

The definition of sudden infant death syndrome (SIDS) is 'the sudden death of an infant under 1 year of age which remains unexplained after the performance of a complete postmortem examination and examination of the scene of death.'

### **Incidence**

Over 300 babies die of cot death or SIDS in the UK each year – 0.4/1000 live births.

Many hypotheses have developed about the causes of SIDS. The search for an individual cause has shifted towards a more complex model. It seems likely that SIDS is the result of an interaction of risk factors – developmental stage, congenital and acquired risks and a final triggering event.

### **Established risk factors for SIDS**

- Age 4–16 weeks
- Prone sleeping position and side sleeping position<sup>4</sup>
- Overheating/overwrapping
- Soft sleeping surfaces
- Fever/minor infection
- Bed sharing with parents (contraindicated if parent has had alcohol, smokes, has taken sedative medication or feels very tired)
- Maternal smoking (ante- and postnatal)<sup>5</sup>
- Low maternal age
- High birth order
- Low birthweight
- Preterm delivery
- Medical complications in the neonatal period
- Social deprivation

- Male sex

## **Protective factors for SIDS**

- Supine sleeping position
- Separate cot
- Appropriate environmental temperature
- ? pacifier (dummy) use (may prevent baby sleeping deeply)
- Stop smoking

The death of any child should be managed in accordance with the Child Death Review process. Each hospital should have its own protocol for dealing with SIDS, which should be adhered to.

Multiagency working is essential. The following are general guidelines:

- Contact consultant paediatrician immediately
- Ensure that parents have a member of staff allocated to them and an appropriate room in which to wait
- Baby should be taken to appropriate area within A&E and **not** to the mortuary
- Initiate resuscitation unless it is evident that baby has been dead for some time (e.g. rigor mortis or blood pooling)
- Parents should have option of being present during resuscitation with nurse supporting them throughout
- Take brief history of events preceding admission, including baby's past illnesses, recent health and any resuscitation already attempted; identify any predisposing factors for SIDS
- Consultant should decide, in consultation with parents, how long resuscitation should be continued for (it is usual to discontinue if there is no detectable cardiac output after 30 minutes)
- Once baby has been certified dead, consultant paediatrician should break news to parents, with support nurse present
- Explain to parents the need to inform the coroner and initiate the Child Death Review process

## **Physical examination**

Carried out by most senior paediatrician present as soon as resuscitation has been completed/abandoned. Need to record the following:

- Baby's general appearance, state of nutrition and cleanliness
- Weight, and position on centile chart
- Rectal temperature
- Marks from invasive or vigorous procedures such as venepuncture, cardiac massage
- Any other marks on skin
- Appearance of retinas
- Lesions inside mouth
- Any signs of injury to genitalia/anus

## **Further action within A&E**

- Inform child death coordinator who will initiate child death review process
- Keep all clothing removed from baby in labelled specimen bags because it may assist the pathologist and may be needed for forensic examination
- Inform coroner's office and discuss collection of further laboratory specimens, take photographs and mementoes such as lock of hair or hand- and footprints
- Arrange for skeletal survey
- Contact Coroner's Office and request them to instruct a specialist paediatric pathologist for the postmortem examination
- If there are any concerns re suspicious death contact the police urgently

## **Taking of samples**

In some centres all samples are taken *post mortem*; however, in others some or all of the following should be taken within A&E:

- Blood for urea and electrolytes, full blood count, blood culture, toxicology (clotted sample)
- Metabolic screen including amino and organic acids, oligosaccharides, blood spot on Guthrie card (for MCAD)
- Chromosomes (if dysmorphic)
- Lumbar puncture
- Nasopharyngeal aspirate, swabs (as appropriate) for bacteriology, suprapubic aspirate for urine microscopy, culture and sensitivity
- Consider skin and muscle biopsy

## **Support for family**

- The Child Death Review doctor and/or nurse will arrange an urgent home visit
- Ensure that the family have Foundation for Study of Infant Death leaflet and helpline number and Department of Health leaflet on postmortem examinations
- Offer to put in touch with local support organizations
- If mother was breast-feeding discuss suppression of lactation
- If baby was a twin recommend admission/investigation of surviving twin
- Ensure that family have telephone numbers of appropriate members of hospital team
- Offer to organize psychological support for older siblings
- Give details of counselling services
- Arrange transport home

## **Communication checklist**

The following should be informed as soon as possible about the baby's death:

- Child death coordinator



- Coroner
- Coroner's officer
- Police
- Family doctor
- Health visitor
- Social worker
- Medical records
- Other paediatric colleagues previously involved in care
- Immunization office

## Follow-up arrangements

For all unexpected child deaths a home visit with the child death nurse and/or doctor is organized. The police may also join the same visit. Subsequent follow-up arrangements differ but parents must be supported and given the opportunity to discuss management and postmortem results. A post death planning meeting will be held as part of the Child Death Review process and a report prepared for their overview panel. A debrief should be held for members of clinical staff.

## 23. ACCIDENT PREVENTION

Around 400 children per year die as a result of accidents in England and Wales and several thousand others suffer serious injuries.

Examples of how mortality and morbidity rates may be reduced include:

- Use of cycle helmets and car restraints (reduce severity of injury in road traffic accidents)
- Urban safety measures (e.g. crossing patrols, traffic redistribution schemes, improving safety on individual roads)
- Use of home safety devices (e.g. smoke detectors, stairgates, thermostat control of hot water)

Studies have established that educational programmes alone are not successful in preventing accidents and that to reduce accidents the educational material must be accompanied by:

- targeting the families most at risk of accidents
- home visits
- free distribution of devices such as smoke alarms

## 24. FURTHER READING

Baroness Kennedy QC (2004). *Sudden unexpected death in infancy*. A report from the working group of the Royal College of Paediatrics and Child Health and the Royal College of Pathologists.

Department of Health (1996). *Immunisation Against Infant Disease*. London; HMSO.

- Department of Health and Home Office (2003). *The Victoria Climbiè Inquiry, Report of an Inquiry by Lord Laming*, Cm. 5730. London; HMSO.
- Foundation for the Study of Infant Deaths. 'Responding when a baby dies' campaign.
- FSID. *Sudden Unexpected Deaths in Infancy; suggested guidelines for accident and emergency departments*. London; Foundation for the Study of Infant Deaths. Available at; [www.sids.org.uk/fsid](http://www.sids.org.uk/fsid).
- National Institute for Health and Clinical Excellence (2004). *Eating Disorders; Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders*. London; NICE.
- National Institute for Health and Clinical Excellence (2005). *Depression in Children and Young People. Identification and management in primary, community and secondary care*. London; NICE.
- Royal College of Paediatrics and Child Health (2005). *Evidence Based Guideline for the Management of CFS/ME in Children and Young People*. London; RCPCH.
- Rutter M (2002). *Child and Adolescent Psychiatry – Modern approaches*. Oxford; Blackwell Science.
- Websites**
- Foundation for Study of Infant Deaths (FSID): [www.fsid.org.uk](http://www.fsid.org.uk)
- Hearing screening: <http://hearing.screening.nhs.uk>
- Vision testing and screening in young children: [www.patient.co.uk](http://www.patient.co.uk)
- Autism: [www.cdc.gov/ncbddd/autism](http://www.cdc.gov/ncbddd/autism)
- Child development: [www.cdc.gov/ncbddd/childdevelopment/index.html](http://www.cdc.gov/ncbddd/childdevelopment/index.html)

---

# Chapter 3

## Child Protection and Safeguarding

*Joanne Philpot and Ruth Charlton*

---

### CONTENTS

#### 1. Definition

#### 2. Physical abuse

- 2.1 History taking
- 2.2 Predisposing factors
- 2.3 Examination
- 2.4 Types of injury seen in physical abuse
- 2.5 Investigation
- 2.6 Management of abuse/suspected non-accidental injuries
- 2.7 Specific presentations of abuse/non-accidental injury

#### 3. Sexual abuse

- 3.1 Presentation
- 3.2 Examination and physical signs
- 3.3 Investigation
- 3.4 Management
- 3.5 Long-term complications

#### 4. Emotional abuse

#### 5. Neglect

#### 6. Fabricated or induced illness

---

# Child Protection and Safeguarding

---

## 1. DEFINITION

The term ‘safeguarding’ is preferred to ‘child protection’ because it is broader and encompasses preventive strategies and approaches. It is defined as:

The process of protecting children from abuse or neglect, preventing impairment of their health and development, and ensuring they are growing up in circumstances consistent with the provision of safe and effective care that enables children to have optimum life chances and enter adulthood successfully.

This definition applies to all children and young people who have not yet reached their eighteenth birthday, including unborn children. All doctors who see children and young people have a responsibility to protect children and young people as outlined in *Good Medical Practice*. New guidance (‘Protecting children and young people: the responsibilities of all doctors’) is currently under development by the General Medical Council (GMC) and gives more detailed guidance on how doctors can fulfil their duty to protect infants, children and young people who are living with their families or away from home.

The term ‘child protection’ can be used to refer to the activity that is undertaken to protect specific children who are or at risk of suffering serious harm. Sadly, in the UK up to 100 children per year die as a result of non-accidental injuries.

Other useful definitions are as follows:

### **Child in need**

This term is applied to children defined as being in need under section 17 of the Children Act 1989, whose vulnerability is such that they are unlikely to reach or maintain a satisfactory level of health or development, or their health or development will be significantly impaired without the provision of services. This can also apply to disabled children.

### **Significant harm**

Some children are in need because they are suffering or likely to suffer significant harm. This is the threshold that justifies compulsory intervention in family life in the best interest of children.

## **Types of abuse**

Physical injury may be inflicted deliberately or by failure to provide a safe environment.

Neglect is the persistent failure to meet a child's basic physical and/or psychological needs to an extent that is likely to result in serious impairment of the child's health or development, e.g. inadequate provision of food, shelter or clothing, failure to protect from physical harm or danger. It also includes failure to ensure adequate care takers and failure to ensure appropriate access to medical care or treatment, as well as unresponsiveness to a child's basic emotional needs.

## **Emotional abuse**

This is the persistent emotional ill treatment of a child such as to cause severe and persistent adverse effects on the child's emotional development. Although some degree of emotional abuse is involved in all types of ill treatment of a child it may occur alone.

## **Sexual abuse**

This involves forcing or enticing a child or young person to take part in sexual activities, including prostitution, whether or not the child is aware of what is happening. This may involve physical contact (e.g. rape or oral sex) or non-contact such as watching pornographic material.

The potential for abuse should also be recognized (e.g. another sibling previously harmed).

## **2. PHYSICAL ABUSE**

There are features that can be elicited during history taking and examination which may increase the risk there has been harm to a child; however, the absence of these should not falsely reassure clinicians.

### **2.1 History taking**

A full and comprehensive medical history should be taken whenever a child or young person is seen by clinical staff.

#### **Key points when taking a history and abuse/non-accidental injury is suspected**

- Consider taking the history directly from the child even without the consent of the carer
- Ask detailed questions re any mechanism of injury, e.g. how did child fall, how far, on to which

surface, who witnessed, etc.

- Record any difference of medical opinion
- Ensure that all notes are comprehensive/contemporaneous (include content of all telephone calls, handovers, etc.)
- Ask about previous admissions/attendances to other hospitals and obtain/validate information
- Within a given location work from one set of medical notes
- Where relevant/possible gain information from multiple sources, e.g. school, GP, health visitor

Concerns are particularly raised by the following:

- Injuries in an infant
- Vague, unwitnessed, inconsistent, discrepant history
- Time delay in presentation
- Unconcerned/aggressive carers
- Inappropriate response in child (e.g. didn't cry, felt no pain)
- Presence of other injuries
- Child/family known to social services, child protection plan in place
- Previous history of unusual injury
- Repeated attendance/presentation

## 2.2 Predisposing factors

Social and family factors predisposing to abuse:

- Young, immature, lonely and isolated parents
- Poor interparental relationship
- Substance abuse in parent
- Parents who had rejection, deprivation or abuse in their childhoods
- Parents with learning difficulties
- History of difficult pregnancy
- Early illness in child
- Difficult behaviour in child

## 2.3 Examination

All children in whom any form of abuse is suspected should have a full and comprehensive examination, which should include assessment of growth and development as well as looking for physical injuries. The child should be fully undressed and examined in a warm, secure environment by an appropriately experienced doctor. Careful charting of injuries is imperative using body maps as needed. Certain injuries are 'typical' in abuse, as follows.

## 2.4 Types of injury seen in physical abuse

### **Bruises**

Bruises are uncommon in children under 1 year especially if not mobile; bruises of different ages or finger-shaped bruises, bruises on head, face and lumbar region, bruising around wrists and ankles (swinging), bruising inside and behind pinna (blow with hand) and ring of bruises (bite mark) should all raise concerns. Two black eyes may indicate blood tracking down after a significant injury to the forehead. Accidental bruises are uncommon in all ages on the buttocks, neck, hands, trunk and lower jaw. In contrast bruises to the front of the body and over bony prominences are more likely to be accidental. Differential diagnosis of bruising includes bleeding disorder, meningococcal sepsis Henoch–Schönlein purpura and mongolian blue spots (most common on buttocks/lower back in those of Asian origin).

### **Fractured ribs**

Unless major trauma or underlying bone disease very suspicious (particularly in younger children) of abuse. May be caused by shaking.

### **Skull fractures**

Whether accidental or non-accidental, these require significant force. Linear parietal fractures are the most common accidental or non-accidental fracture. Features of particular concern include: occipital fractures, depressed fracture, growing fracture, wide fracture, fracture crossing suture line, history of fall less than 3 feet.

### **Femoral fractures**

In children who are not independently walking these are suspicious of abuse.

### **Fractures of humerus**

Spiral fractures are uncommon and commonly linked with abuse.

### **Epiphyses torn off**

This may indicate swinging.

### **Metaphyseal fractures**

These are rare and may indicate abuse particularly in those under 2 years.

**Important differentials to consider in diagnosis of non-accidental fractures**

- Accidental injury
- Osteopenia including prematurity, chronic illness, e.g. renal disease, severe growth faltering
- Osteogenesis imperfecta
- Iatrogenic, e.g. post-interosseous insertion, also described after holding neonates for blood sampling
- Malignancy
- Infection
- Vitamin D deficiency (rickets) – more common than other vitamin deficiencies and highlights importance of careful dietary history
- Vitamin A and vitamin C deficiency (uncommon)
- Copper deficiency

## **Burns**

Burns and scalds are common in children and most are accidental; however, they may involve cases of inadequate supervision/neglect. Hot drinks cause most accidental injuries, with heaters, fires, cookers, fireworks, candles and sunburn also being implicated. Concerns that burns are non-accidental should be raised by presence of small circular burns which may be caused by cigarettes, burns or scalds to both feet or buttocks; these raise the possibility of immersion injury and clearly demarcated burns where a hot object has been applied to skin.

## **Torn frenulum**

This may indicate direct blow to mouth or forced feeding.

## **Perforated eardrum**

This can be caused by slap or blow to side of head.

## **Strap or lash marks**

## **Nail injuries**

## **Marks from strangulation**

## **Subdural haematoma**

This may be caused by shaking (see below under Management of abuse/suspected non-accidental head injuries).

## **Retinal haemorrhages**

This may be caused by shaking (see below under Management of abuse/suspected non-accidental



head injuries).

## Multiple injuries and injuries at different ages

### Estimating ages of bruises and fractures

This cannot be accurately done and should not be relied on as part of the assessment.

## 2.5 Investigation

These will be dictated by clinical presentation but may include the following:

- Full blood count, clotting, bleeding time
- Radiograph/skeletal survey: must be performed and reported by specialist paediatric radiologist. Should be considered particularly in child under 2 years. May need to be repeated if first survey negative, bone scan not available and bony injury suspected
- Bone scan: consider particularly if bony injury suspected but not confirmed on initial skeletal survey
- Cranial imaging: ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI) as clinically indicated. Ultrasonography not always able to pick up subdurals. CT of the brain often included with all skeletal survey requests in under 2 year olds
- Others: calcium, phosphate, alkaline phosphatase, vitamin D, copper, DXA (dual energy X-ray absorptiometry) scan, acylcarnitines + urinary organic acids (if subdural haemorrhage)

### When to consider a skeletal survey

- Suspected physical abuse
- Unexplained neurological symptoms including apnoeas, seizures, reduced consciousness
- Intracranial injury (when no history of significant accidental trauma)
- As part of investigation of siblings where abuse has been identified in other child in family unit
- Child dying in unusual/unexplained circumstances

## 2.6 Management of abuse/suspected non-accidental injuries

- Put the interests of the child first
- Adhere to local protocols
- If suspicion of non-accidental injury, early senior decision-making with involvement (as needed) of named/designated nurse/doctor
- Additional information from school, GP other professionals
- Check with social care if child is subject of child protection plan
- Consider investigations as appropriate to clinical presentation
- Piece together 'jigsaw' of information from multiple sources
- Early liaison/referral to social services if suspected abuse (in most cases parents/carers should be

told that referral is taking place)

- Telephone referrals should be followed by written referral within 48 hours and written referral should be acknowledged within 1 working day. Social care will then initiate and lead on assessment as needed
- Secure place of safety for child – consider hospital admission if injury/illness require or it temporary safe place needed

### **Immediate referral to children's social care and/or police**

- Suspected abuse or neglect where concern that child and/or siblings unprotected
- Serious abuse witnessed

### **Immediate referral to police if**

- Allegations of recent rape or sexual assault
- Dead or severely injured children where abuse is thought likely (preservation of crime scene)
- Threatened removal from hospital where child is thought to be in danger

## **Strategy meeting**

This is a formal gathering of individuals with a legitimate interest in the child and family and usually includes social services, police and other relevant agencies including health. Where needed this is convened urgently. The meeting allows exchange of relevant information and decision-making about further management which will include decisions about immediate safeguarding actions needed, e.g. where and by whom the child should be looked after, whether any criminal investigations should be initiated and what information should be shared with family.

After the strategy meeting decisions will be taken as to whether any further involvement is needed by children's social care and/or the police. Further meetings and information may result in a child protection plan being put in place. This will then be subject to further and ongoing review.

Although publications such as *What to Do if You're Worried a Child is Being Abused* (Department of Health 2003) describe in detail processes that should be followed this should not be seen as a substitute for discussing all such cases and concerns with senior clinicians.

## **2.7 Specific presentations of abuse/non-accidental injury**

### **Head injury**

The presentation is variable and ranges from sudden death, or seizures, to feeding difficulties. The varied potential presentation highlights that non-accidental head injury (NAHI) should be considered in any child who suddenly collapses. Although most common in infants under 6 months, NAHI can be seen in older children too. The mortality rate and rate of long-term sequelae in survivors are high.

Controversy surrounds the mechanisms of injury in NAHI; however, the conventional view is that the injuries are caused by either impact to the head or severe repetitive rotational injury. This can result in the development of:

- Brain injury – of the brain substance directly by trauma or hypoxic or ischaemic change
- Intracranial bleed – note that, although subdural, subarachnoid and intraventricular/parenchymal bleeds are typical, an extradural bleed is rare
- Skull fracture
- Retinal haemorrhage
- Other bruising/lacerations to body/limbs/scalp/face
- Rib or long bone fractures
- Spinal cord injury

A full history and examination should be taken as above and, of particular note, a fontanelle, head circumference and retinal examination should be done. Guidance suggests that the first line in neuroimaging is CT followed up with MRI where needed and skeletal survey. It is recommended that, in all children under 2 years in whom a skeletal survey is requested, a CT of the brain should also be performed.

### **Potential differential diagnosis of NAHI that must be considered/excluded**

- Severe accidental injury – highlights the importance of careful history taking and information gathering
- After birth retinal haemorrhage and subdural haemorrhage occur but resolve within the neonatal period
- Bleeding disorders – ensure that these are excluded
- Other causes of subdural haemorrhage – glutaric aciduria type 1, postoperative, hypernatraemic dehydration, rare congenital malformations

Management is as described above; however, such infants are usually managed in tertiary units and early strategy discussions will determine whether criminal investigation should be pursued.

## **Poisoning**

This is rare but consider if signs and symptoms are difficult to explain. Blood and urine will need to be screened.

## **Intentional upper airway obstruction**

This is a difficult and controversial area because it may be impossible to distinguish intentional airway obstruction from other causes of sudden and unexplained death in infancy (SUDI). In many cases there are no clinical signs evident externally and for those who survive the sequelae may be significant. Presentation can be with the following:

- Sudden death
- Acute life-threatening event (ALTE)
- Apnoea/transient respiratory difficulty
- Cyanotic spells
- Recurrent seizures
- Other unexplained collapse/illness
- Bleeding from nose or mouth

The presence of blood around the mouth in an infant who has survived ALTE should raise particular concerns, as should petechiae on the neck and conjunctival haemorrhage. At-risk factors from the past or family history should also be considered

## 3. SEXUAL ABUSE

### 3.1 Presentation

Sexual abuse may present in many ways:

- Allegations by a child or adult
- Injury to genitalia or anus (including bleeding or sexually transmitted infection)
- Unexplained recurrent urinary tract infection
- Sexual explicitness in play, drawing, language, behaviour (including excessive masturbation)
- Sudden or unexplained changes in behaviour, e.g. sleep disturbance, loss of trust in individuals close to them, overdose, running away from home
- Psychosomatic indicators including recurrent headache, abdominal pain, enuresis, encopresis, eating disorder
- Pregnancy
- Sexually transmitted infection

### 3.2 Examination and physical signs

The examination should take place in a quiet, child-centred room with appropriate facilities. Examination for suspected abuse requires a doctor with specific expertise and training, and facilities for colposcope and photo documentation. Older children may prefer a doctor of the same sex. Consent is required before the examination and a forensic pack will be needed if the last assault was within 72 hours.

The signs elicited must be taken in the context of the complete examination. Careful documentation should be made in the form of sketches and photographs. A full general examination should also be performed because there is a significant chance of coexisting physical abuse. Remember that up to 50% of children subject to sexual abuse have no abnormal physical signs.

## Specific features to look for in girls

- Reddening, bruising, lacerations and swelling of labia, perineum and vulva
- Vaginal discharge (comment on quantity and colour – on its own not strongly suggestive of abuse)
- Hymenal opening – comment on size, margins, tears (>0.5 cm suspicious of sexual abuse, >1 cm greater likelihood)
- Posterior fourchette – laceration/scars
- Vaginal examination – only in older girls if clinically indicated

## In boys

- Penis – bruising, laceration, scars, burns
- Perineum – reddening, bruising
- Scrotum – bruising, reddening, burns
- Anal examination

Examine young children on carer's knee and older children in left lateral position.

Rectal examination rarely necessary; instead inspection should determine the presence or absence of acute signs such as:

- Swelling, reddening, bruising, haematoma, laceration or tears of anal margin
- Spasm, laxity and dilatation of anal sphincter
- Dilatation of perianal veins

## 3.3 Investigation

It may be appropriate to screen for sexually transmitted infections and to send forensic swabs for analysis of semen/grouping. These should be handled in a forensic way.

## 3.4 Management

### Clinical

- Emergency contraception/antibiotics for sexually transmitted infections as needed
- Consider possibility of HIV infection
- Treat and deal with medical issues identified during assessment

### Non-clinical

- Follow guidelines as outlined in management of suspected non-accidental injury.

### 3.5 Long-term complications

This includes post-traumatic stress, suicidal behaviour, psychiatric illness, problems with relationship and sexual adjustment.

#### Differential diagnosis of vaginal bleeding

- Trauma – sexual abuse or accident such as straddle injury
- Precocious puberty
- Skin disease, e.g. lichen sclerosis et atrophicus
- Rare anatomical abnormalities

#### Differential diagnosis of rectal bleeding

- Fissures (constipation or abuse)
- Infective diarrhoea
- Inflammatory bowel disease
- Polyp

## 4. EMOTIONAL ABUSE

A wide variety of symptoms may result from emotional abuse, rendering recognition of this difficult and emphasizing the importance of working closely with colleagues in the Child and Mental Health Services (CAMHS) and psychology.

In babies this may include feeding difficulties and poor weight gain, crying excessively or conversely being excessively quiet and non-demanding. Similarly, in toddlers, symptoms range from being quiet and clingy to being overactive with a bad temper.

Older children may present to clinicians with difficulties in school performance, antisocial or difficult behaviour, wetting, soiling or developmental delay, or regression. Growth delay may be seen and, if investigated, suboptimal growth hormone production may be noted (as a consequence of emotional neglect/abuse).

As indicated above, management involves close working between professionals in social care, health and psychological medicine.

## 5. NEGLECT

Neglect can manifest in a multitude of different ways to different agencies. Presentation to health services includes: multiple A&E attendances with injuries, non-concordance with treatment plans for health conditions or failure to present for medical intervention with untreated medical conditions, failure to take up routine immunisations, failure to thrive, behavioural changes ranging from craving

attention from adults to being shy and withdrawn, difficult/challenging behaviour and school failure. As above, a multiprofessional/multiagency approach to assessment and management is required.

## 6. FABRICATED OR INDUCED ILLNESS

This used to be termed ‘Munchausen syndrome by proxy’ and may coexist with other forms of child abuse. The spectrum of presentation is wide and includes suffocation, non-accidental poisoning and sudden infant death.

Typically the child presents multiply for medical assessment and may have multiple procedures and investigations performed. Although uncommon it should be considered in any child with inconsistent symptoms/signs, unexplained or prolonged illness and poor response to treatment. Features in the history that may raise concerns about fabricated or induced illness (FII) include the following:

- Family history of unexplained illness or death
- History given of deaths/illnesses that are not substantiated
- Actions of parents/care givers not appropriate for symptoms described

Accurate history taking and reconciliation from all professionals involved are pivotal in making a diagnosis.

Management often requires hospital admission/investigation. Early multiprofessional referral to police, social workers and mental health teams is required, in addition to medical and nursing input and assessment. Referral to other agencies above should not wait until the diagnosis is proved and early multiagency strategy planning is critical.

## FURTHER READING

Department of Health (2003). *What to Do if You're Worried a Child is Being Abused*. London: DH.

General Medical Council (2006). *Good Medical Practice*. London: GMC.

---

# Chapter 4

## Clinical Governance

*Robert Wheeler*

---

### CONTENTS

- [1. A brief history](#)
- [2. The influences bearing on an NHS trust](#)
- [3. Patient safety](#)
- [4. Patient experience](#)
- [5. Clinical outcome and experience](#)
- [6. Education, appraisal and revalidation](#)
- [7. Conclusion](#)
- [8. References](#)



---

# Clinical Governance

---

At the time of writing, the Government in England is pausing, to reflect on the national reaction to the Health and Social Care Bill, regarded variously as an essential measure or a disastrous experiment by equally vociferous factions. From the perspective of clinical governance, it is an interesting historical moment, because it demonstrates how an incoming government can simply flush away expensive institutions, if it wishes, in order that the governance of governance can better accord with a political vision. In reality, the expected demise of the National Patient Safety Agency (NPSA) and the National Information Governance Board will have little noticeable effect on those of us who look after patients, because the functions of these bodies will be subsumed into the overarching Care Quality Commission (itself a descendant of the Healthcare Commission), or its derivatives. But these transitions are occurring all the time, unbeknownst to most of us. In this existence of two parallel worlds, one group (usually comprising senior nurses who have moved away from clinical practice) is entirely immersed in the machinations of governance, dedicating substantial efforts to activities described by mysterious acronyms that are of utterly crucial importance to a trust's relationship with the Department of Health. At the same time, and in the same hospital, the other group (clinicians) will be treating patients, and providing data for the first group to use to assuage the scrutiny under which they live their daily lives. This chapter tries to demonstrate the pressures on all servants of a trust, whether managerial or clinical, in 'delivering' clinical governance. One can then better sympathize with one's colleagues in the parallel world that is the trust's governance department, and also understand how both the patient and the health service can benefit from this method of quality control.

## 1. A BRIEF HISTORY

Since the inception of the NHS (National Health Service Act 1946) the practice of medicine was governed by professional judgement. Clinical decisions were made on the basis of knowledge accumulated during an apprenticeship, and this knowledge was validated by certification from The Royal Colleges. Compulsory registration with the General Medical Council (GMC) was assumed to provide an assurance of fitness to practise and propriety, together with sanctions for transgressions.

Clinical practice itself, based on written and oral precedent, was seen as an evolving body of knowledge, against which new information could be evaluated.

These arrangements lasted, with varying degrees of satisfaction depending on the commentator, for

more than 40 years. However, because of inexorable rise of the cost of litigation,<sup>1</sup> the drug budget and institutional catastrophes,<sup>2,3</sup> there was a profound shift from the internal standard of medical self-regulation to an externally imposed regulatory apparatus, conforming to standards derived from state control.

With the advent of the hospital trusts, politicians took renewed interest in quality issues. The Conservative administration had already coined the phrase ‘clinical governance’ by 1996, and the advent of the New Labour government in 1997 confirmed clinical governance as the byword for quality assurance and enforcement. A White Paper followed,<sup>4</sup> translating the concept into several national developments, with a mission to set or enforce standards. By late 1998, when interested parties had recovered from the onslaught of novel watchdogs, words and concepts, a steady stream of contradictory literature had begun to flow at national and local level, all trying to make sense of what ‘clinical governance’ actually meant.

The concept of governance was adapted from industry,<sup>5</sup> meaning ‘to control and direct, with authority’.<sup>6</sup> It was originally conceived as being based upon seven central ‘pillars’: risk management; clinical effectiveness; education and training; patient and public involvement; using information; research and development; management and manpower. Organized within these broad categories, any aspect of clinical practice that could be regarded as pertaining to ‘quality of care’ could be subjected to intense scrutiny. Although the pursuit of ‘quality’ now seems uncontroversial, the reaction by doctors was not universally favourable,<sup>7</sup> many feeling that governance added no further value to their standard of care, which already exemplified many of the principles contained within the pillars. This conflict of understanding may have arisen from the necessity for clinical governance to be delivered by a team, rather than by an individual doctor. Consultants considered that they still retained ‘ownership’, the basis of continuity of care, which remained their touchstone of ‘quality’. As time has passed, the resistance to this change has all but melted away.

However, regrettably, the burden of *implementation* of clinical governance has now been taken on largely by the nursing staff, arguably because of doctors’ reluctance to do so. There are notable and honourable exceptions to this generalization, but review of the staffing of your local clinical governance arrangements may reveal a level of medical engagement that is disproportionately low, when considering the number of doctors in your trust.

## 2. THE INFLUENCES BEARING ON AN NHS TRUST

Currently, and even following the implementation of whatever creature is born from the Health and Social Care Bill, NHS trusts and their derivative foundation trusts will be controlled by the Care Quality Commission (CQC). Already the cornerstone of quality control in the NHS, its absorption of the functions of other arms’ length bodies of the NHS, such as the NPSA, will make it the main controller of safety and quality within the NHS. The CQC achieves this through inspections of hospitals, and by demanding that an exhaustive series of standards are complied with, which range throughout all clinical activities to which a patient may be exposed. Closely allied to the CQC is Monitor, an organization created to ensure that the financial aspects of health care are equally well

governed. As NHS trusts are inexorably converted to foundation trusts, the role of Monitor (in financial governance) will mirror that of the CQC in clinical governance.

Another separate influence is exerted by the NHS Litigation Authority (NHS LA). This organization assesses the financial risk faced by the NHS as a whole, and defends clinical negligence cases where deemed appropriate. Each trust that subscribes to the Clinical Negligence Scheme for Trusts (CNST) pays an annual subscription for this service and the NHS LA acts as an insurer, settling successful claims on behalf of the Scheme's members. The NHS LA provides an incentive for the CNST members. If a trust can 'pass' one of three thresholds, it will secure a reduction of 10, 20 or 30% of the insurance premium, depending on the threshold passed. This assessment of the trust's risk management is performed during a visit by inspectors, but the trust will have been striving for months or years to meet the numerous highly prescriptive 'standards' set by the NHS LA. These standards are imposed in order to reduce the risk that patients are harmed, that they will thus be less likely to become claimants and that, of course, the trust will 'pass' the inspection at the chosen threshold.

The burden of complying with the CQC, Monitor, the NHS LA and other agencies that will be mentioned later falls initially upon the chief executive of the trust; he or she will then devolve this to the medical director, the head of nursing and those in charge of finance. Furthermore, failure to comply with the demands of these agencies will lead to attention from the Department of Health, and ultimately a Health Minister, anxious to avoid a blemish on his or her political ascendancy. All of this weight will rapidly descend on to the shoulders of the hapless clinical governance staff, whose jobs depend upon compliance with the various standards.

And the standard setting is not monopolized by these key organizations. Primary care trusts (while they still exist) have a contractual obligation (to those who fund them) to ensure competent governance in clinical areas under their nominal control. As illustrated later, they, in turn, exercise their contractual influence over the hospitals in their domain to fulfil this obligation. Others also bring pressure to bear: coroners, fire authorities, environmental health, HFEA (Human Fertilisation and Embryology Authority), HTA (Human Tissue Authority), counterterrorism, counterfraud, GMC, NMC (Nursing and Midwifery Council), radiation protection, cellular pathology accreditation, MHRA (Medicines and Healthcare products Regulatory Agency), and many more 'partners', 'shareholders', 'stakeholders' (choose your own jargon), will be pointing out that their particular standards need to be adhered to immediately, if not earlier, and that this should be achieved under the broad control of *clinical governance*.

This may give you some appreciation of what your clinical governance department has to put up with, and why, on occasions, it is simply desperate for some somewhat obscure data that have no apparent clinical value. In reality, the job of someone in your trust (at a very much lower pay scale than your own) depends upon it.

The division of clinical governance now broadly divides into patient safety, patient experience, and clinical outcomes and effectiveness. Information governance and education, although still of great importance, are now sometimes seen as contributors, rather than ends in themselves. The principal three disciplines went through a stage of being firmly centralized at the heart of the trust, from where these activities were coordinated. More recently, certainly in the bigger organizations, a restructuring

into divisions has made it possible to devolve these functions to divisional level; thus a ‘women and children’s’ division is likely to deal with the daily business of governance, but will still send data to a central coordinating governance department, who will liaise directly with the agencies mentioned above.

### 3. PATIENT SAFETY

This web of communication can best be discerned within the governance discipline of ‘patient safety’, formerly known as ‘risk’. Risk describes anything that may put the patient, clinician or parent in harm’s way. This may be as specific as the risk of injecting the wrong chemotherapy into the spine, or as banal as ensuring that the doors to the outpatients do not trap children’s fingers. Risks can thus come from the spectrum of practice, and the principle of management is to identify them before they cause damage. The reporting of risks is now commonplace, usually achieved with the use of the ubiquitous adverse incident form. Those who have filled one in will be familiar with the details that are required: of the incident in question; witnesses and participants; and of the inherent risk assessment incorporated in the form. This combines, within a matrix, the consequences (ranging from ‘none’ to ‘catastrophic, death’) with the likelihood of recurrence (ranging from ‘rare’ to ‘certain’). The product of the matrix is a risk assessment encoded in colours, ranging from a *very low* ‘green’ risk to an *extreme* ‘red/red’ risk. This categorization is important, because the trust’s reaction to the risk is directly proportionate to its severity.

All risks need to be reported, usually by the trust’s governance apparatus, to the National Reporting and Learning Service (NRLS). This organization, established in 2003, provides a unique national database for incidents affecting patient safety, and is widely recognized<sup>8</sup> as a world leader, giving an opportunity to identify systemic errors that may be avoidable in the future. The NRLS is a division of the NPSA, but it seems likely that the NRLS will be incorporated within an as yet ill-defined body, the NHS Commissioning Board. The functions and remit of this Board should be determined as the effects of the Health and Social Care Bill (and then Act) become clearer.

The incidents assessed by the trust as being at the higher levels of severity are subjected to added scrutiny. This may take the form of root cause analysis (RCA), or review by an internal expert ‘serious event’ committee or by a coroner. If the incident meets the local strategic health authority’s (SHA) threshold of seriousness, it will be reported as a Serious Incident Requiring Investigation (SIRI). Worse, if included in the Department of Health’s shortlist (see [www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance)) of 25 ‘very serious, largely preventable patient safety incidents that should not occur if the relevant preventative measures have been put in place’, the incident will be reported as a ‘Never Event’, with serious financial and reputational consequences for the trust (let alone the wretched patient on whom it was inflicted). However, even the apparently prescriptive ‘never events’, which are imposed on trusts as part of a contractual agreement, leave room for interpretation. ‘Wrong site surgery’ was one of the eight points in the core list originally produced in 2009 (see [www.nrls.npsa.nhs.uk/resources/collections/never-events](http://www.nrls.npsa.nhs.uk/resources/collections/never-events)). But what of a wrong level laminectomy? It transpires that this would not qualify as wrong site surgery, because the intention was only to avoid lateralized errors. This does not inspire reassurance that the system is sufficiently flexible to

discourage poor practice.

Perhaps it is not crucial, in approaching the MRCPCH, to be familiar with the jargon in the last paragraph. But the story illustrates the significant subjectivity employed in dealing with risks to our patients. The SHA ‘threshold’ appears to vary across the country, and is ill defined. So trusts, when considering whether their incident has met the SIRS threshold, are unsure of what that threshold is. In the meantime, PCT assessors, anxious both to fulfil their own obligations *and* to enforce a trust’s obligations to the PCT scrutinize reports to the NRLS. They may identify cases that they believe have met the SIRS threshold, and complain that the trust has ‘failed’ so to do. Negotiations then commence.

Thus the appearance of certainty about what is reported; and how it is reported; and what effect the reporting has, is somewhat illusory. There is, however, no doubt at all that this process has created a reporting industry. As we have seen, there may be tangible patient benefit from its product in the NRLS, but it can also be seen that there is some way to go before the system can be considered watertight.

## 4. PATIENT EXPERIENCE

Emerging with the initial tranche of governance themes, what was originally described as ‘patient and public involvement’ has sometimes been elusive in definition. It is easy to identify what it represents, which is a laudable aim for tailoring medical services to the requirements of the patients, rather than making the patient fit in with what proves convenient for the doctor. It also lends itself admirably to politicians, ever anxious to be seen to be *listening* to patients, of affording them *choice*. The difficulty, of course, is to do either of these things in a meaningful way, leading to benefit. Furthermore, there appears to be little or no evidence that these efforts at patient participation create any measurable benefit to the patient.

Trusts have struggled to implement the political agenda of listening to patients. Patient Advocacy and Liaison Services (PALS) have provided a valuable conduit for patients who are distressed or disgruntled by their management in the hands of a trust, and continue to play a vital role clarifying the mysteries of the health service to those who have contact with it. Considerable creativity has resulted in patient forums, although the advent of foundation trusts has made patient and public involvement mandatory. Surveys, focus groups and a variety of methods by which patients feed their comments back to providers, ranging from the distribution of postcards to patients to providing contact numbers for text messaging, have all been tried. One great difficulty is determining what to ask. Although the political demand for patient involvement can be met by simply asking ‘how was your stay?’, the yield of useful information is low, once the problems surrounding car parking, decent food, clean wards and reliably communicative clinicians have been addressed. These are hardly revelations. However, it has become increasingly clear that systematic surveys by experts in the field, such as the Picker Institute (see [www.pickereurope.org/policyprimers](http://www.pickereurope.org/policyprimers)), have filled this gap and, over the last few years, Government, trusts and patient groups have used the data collected to clarify what patients and their relatives need (and want) from their contact with health services.

An interesting aspect of the ‘choice’ element, now implemented nationally, is the rapid enforcement of

the patients' ability to choose where and by whom they should be treated. It remains to be seen whether this will result in improved patient satisfaction or clinical outcome.

## 5. CLINICAL OUTCOME AND EXPERIENCE

The much-publicised medical errors, together with a logarithmic rise in medical negligence litigation, led to calls for measurement of clinical performance. At its most simplistic, it has afforded the Government an opportunity to publish 'league tables' for trusts in such areas as cardiac mortality. Although recognized as a potential oversimplification, this has led the call for trusts to publish the results of their clinical department. Such data are now available, via 'Dr Foster' (see [www.drfoosterhealth.co.uk](http://www.drfoosterhealth.co.uk)). This organization produces data relating to hospital trusts, procedures, consultants and maternity units. Their first consumer guide to health services was published in 2001. This, 'Dr Foster' notes, was 'the first time that comparative adjusted death rates for all NHS hospital trusts had ever been published'. Their recent hospital report covers deaths in hospital, stroke, orthopaedic care, urological care and the recording of safety incidents, notably those involving venous thromboembolism (see [www.drfoosterhealth.co.uk/docs/hospital-guide-2010.pdf](http://www.drfoosterhealth.co.uk/docs/hospital-guide-2010.pdf)). Independent of external organizations, clinicians have for many years used audit to ensure that their local results compare favourably with an established gold standard, thus measuring whether the local unit is at variance with the standard, modifying practice to improve results and then remeasuring (re-auditing) to ensure that the modification has achieved the desired result.

Any conceivable clinical intervention has potential for audit and this has been a highly satisfactory tool as a measure of clinical performance, provided that it is used appropriately and correctly. Audit programmes can be integrated with other aspects of clinical governance. If a clinical intervention is identified as a risk as a result of either adverse incident reporting or a cluster of similar complaints, then this gives an ideal opportunity for audit.

On a larger scale, the National Institute for Health and Clinical Excellence (NICE – see [www.nice.org.uk](http://www.nice.org.uk)) has employed similar techniques to provide clinicians with robust evidence that therapies and interventions are efficacious and cost-effective. It should be acknowledged that the latter criteria, of cost-effectiveness, has led to ferocious opposition to some of NICE's judgements, on behalf of patients who felt disadvantaged as a result of treatments that were not deemed to be cost-effective. It could well be argued that, faced with spiralling costs for pharmaceuticals, the Government's creation of organizations such as NICE was largely motivated by the wish to limit NHS costs, a theme that feels contemporary in 2011. Notwithstanding this, the current remit of NICE appears to have turned away from determining whether an intervention is cost-effective, but it seems inevitable that a financial threshold for whether a drug (or treatment) can be paid for by the NHS will continue to be of crucial importance. At the time of writing, PCTs are attempting to identify therapies that they will not pay for. Attempts are being made to persuade the High Court that denial of bariatric surgery is contrary to patients' human rights, and this claim has failed (see [www.anhourago.co.uk/show.aspx?l=8362077](http://www.anhourago.co.uk/show.aspx?l=8362077)); one way or another, there seems little doubt that the Government will succeed in rationing some aspects of health care.

NICE has developed a series of national clinical guidelines with the intention of securing consistent, high-quality, evidence-based care for NHS patients. Not all guidelines formulated by NICE have been



welcomed by practitioners. The opposition to the guidance on the management of urinary tract infection in children (see [www.nice.org.uk/CG54](http://www.nice.org.uk/CG54)) is particularly memorable – an example of where a spirited opposing medical consensus (see [www.bmj.com/content/335/7616/395.short/reply](http://www.bmj.com/content/335/7616/395.short/reply)) can, at times, effectively challenge a national edict. There remains a belief, by a substantial minority of children's doctors, that the gaps in the evidence supporting the guidelines can lead to unnecessary investigations and a consensus is lacking. Nevertheless, these guidelines are generally of considerable value. Together with a wealth of additional educational text and resources, they are promulgated by NHS Evidence (see [www.evidence.nhs.uk](http://www.evidence.nhs.uk)), acting as an information portal.

To maintain enthusiasm for audit within a department is quite a different matter, partly because some doctors see this merely as a self-fulfilling process. The role of the divisional or trust clinical effectiveness department is crucial in this, because, with its links to patient safety and education, audits that are genuinely worthwhile can be identified and supported by an entire department. A pragmatic approach is a rolling audit, where a topic is chosen that continually poses a clinical challenge; the adherence to the unit protocol for the management of bronchiolitis would be a recurring theme. The audit can be set up along the usual lines, but then the re-audit phases, together with retrospective comparisons and prospective protocol adjustment, can be undertaken by successive generations of junior staff. In this way, audit becomes an integrated part of the working routine, not dependent on additional enthusiasm or drive by the medical team. Ideally, a combination of rolling 'routine' audit, with additional audits reacting to risks, should run simultaneously.

## 6. EDUCATION, APPRAISAL AND REVALIDATION

These elements of governance run in parallel with other activities. Continuing education for doctors has been mandatory for many years. Although there was once optimism that this would be reflected in fixed consultant education sessions, the financial state of the NHS makes this increasingly unlikely. Nevertheless, education is, in many senses, the 'glue' that holds governance together. Lessons learnt from patient safety sources, such as adverse incidents, SIRIs and the like, can be disseminated, as may those identified by patient experience surveys. Educational theory, harnessed to improve and diversify the approach of clinical teachers, will enhance the communication of these important messages.

Assessment (which is a mere observation – a measurement of attendance, workload, waiting times, educational target fulfilment) is a great deal easier to perform than appraisal (a process of valuation, estimating the worth and quality of clinical activity).

This is because the individual can perform assessment themselves; it may involve tedious and time-consuming data collection and form filling, but it is an objective exercise. Appraisal, however, can be performed only by an outsider who shares enough of the appraisee's training to allow pertinent questions to be asked, and relevant feedback to be given. This is equally time-consuming, but potentially threatening and more subjective than assessment. Local appraisal is now elevated to a new level, of *strengthened* or *enhanced* medical appraisal. This will require more engagement from both appraisee and appraisers, but is motivated by the desire to make appraisal more effective.

The need to have an effective form of regular scrutiny of qualified doctors was prominent on the political agenda, prompted by the crimes of Dr Harold Shipman. This in part explains the anxiety of the GMC to produce a workable formula in 2001 to facilitate revalidation of a doctor's original medical registration. It is a tribute to the difficulty of the task that, by 2011, a workable solution has yet to be implemented, although this appears to be imminent. To an extent, this has been delayed by the political rhetoric. Although apparently a convenient moment to incorporate a mechanism to identify potential mass murderers through the revalidation process, it is becoming clear that this is unworkable, and that cyclical revalidation of doctors will be largely based on local appraisal. The local appraisal process remains a matter for individual medical directors, who now take on the additional responsibility of being *responsible officers*, reflecting the devolution of some of the responsibilities of revalidation away from the GMC. It seems that reforms to the laws concerning the registration of death are more likely to reduce the risk of another similar tragedy than the revalidation of doctors, but this remains to be seen.

## 7. CONCLUSION

There is little doubt that hospital patients and clinicians should equally welcome additional supervision of clinical activities. Clinical 'freedom' may seem insufficiently controllable to guarantee adequate quality of care, and it is understandable that any government would wish to demonstrate an augmented quality of care, rather than merely reiterate a financial commitment to health. External regulation has become a cornerstone of the Government's 'third way' in health care.<sup>9</sup> This has been achieved by asking doctors to comply with standards set by NICE, and deterring variance by the employment of agencies such as the CQC and the NHSLA. The product of this alliance is implemented by the clinical governance structure. Residual concerns that the evidence base is unreliable and the individual patient's best clinical interest may not be best achieved by following a guideline produced from an averaged population must be addressed. Effectively enforced 'bullet-point' medicine is likely to interfere significantly with the therapeutic relationship between a patient and doctor.<sup>10</sup> The counter argument is that, from a utilitarian point of view, the rather broad brush approach of clinical governance, *controlling and directing* (the clinicians) *with authority*, may confer the least risk on the greatest number.

But it seems that a workable compromise between what is effective for the population, compared with what will benefit the child in front of you, is emerging.

## REFERENCES

1. Harpwood V. *Negligence in Healthcare*. London: Informa Publishing Group, 2001: Chaps 10, 11.
2. Department of Health. *Report of the Public Inquiry into Children's Heart Surgery at Bristol Royal Infirmary 1984–1995: Learning from Bristol*. Cm5207. London DH, 2001.
3. Department of Health. *The Royal Liverpool Children's Inquiry Report*. London: The Stationery



Office, 2001.

4. Department of Health. *The New NHS – Modern, dependable*. London: The Stationery Office, 1997.
5. Donaldson L. Clinical governance. (Originally Sir Adrian Cadbury, referred to by Clinical Governance.) *Medico-Legal Journal* 2000;**68**: 89–100.
6. Department of Health (1998). *A First Class Service: Quality in the new NHS*. London: Department of Health, 1998.
7. Klein R. *The New Politics of the NHS*, 4th edn. Harlow: Prentice Hall, 2000.
8. Scarpello J. After the abolition of the National Patient Safety Agency. *BMJ* 2010;**341**:1005–6.
9. Walshe K. The rise of regulation in the NHS. *BMJ* 2002;**324**:967.
10. Teff H. Clinical guidelines, negligence and medical practice. In: Freeman M, Lewis A (eds), *Law Medicine: Current legal problems*, vol 3. Oxford: Oxford University Press, 2000: 80.

---

# Chapter 5

## Clinical Pharmacology and Toxicology

*Steven Tomlin*

---

### CONTENTS

#### 1. Pharmacokinetics and dynamics

- 1.1 Absorption
- 1.2 Distribution
- 1.3 Half-life
- 1.4 Hepatic metabolism
- 1.5 Renal excretion
- 1.6 Other clinical considerations

#### 2. Formulation

#### 3. Paediatric dosing

#### 4. Prescribing outside licence

#### 5. Drug monitoring

#### 6. Intravenous management

- 6.1 Maintenance fluids
- 6.2 Monitoring

#### 7. Drugs in pregnancy

#### 8. Drugs in breast milk

#### 9. Toxicology

- 9.1 Paracetamol

[9.2 Iron](#)

[9.3 Tricyclic antidepressants](#)

[9.4 Aspirin overdose](#)

[9.5 Lead poisoning](#)

[9.6 Carbon monoxide](#)

[9.7 Button batteries](#)

## [\*\*10. Further reading\*\*](#)

---

# Clinical Pharmacology and Toxicology

---

The large intergroup variability within childhood has profound consequences on the way in which they handle medicines. This is true in terms of pharmacokinetics and dynamics, but also requires the prescriber to have an appreciation of the physical and psychological variances that may affect medicine use safety and efficacy (e.g. can they swallow tablets, open bottles, read information?).

## 1. PHARMACOKINETICS AND DYNAMICS

- Pharmacokinetics is what the body does to a drug
- Pharmacodynamics is what the drug does to the body

### 1.1 Absorption

- Liquid and intravenous forms of drugs (i.e. those already in solution) are readily absorbed into the body's systemic circulation
- Solid dosage forms (tablets and capsules) and suspensions must first be dissolved in the gastrointestinal tract (dissolution phase) before they can be absorbed, and so absorption is slower
- The term 'bioavailability' is applied to the rate and extent of drug absorption into the systemic circulation

### Oral

#### First-order kinetics

Oral absorption of drugs is often considered as demonstrating first-order kinetics. This is especially true with oral solutions. 'First-order kinetics' implies that the fractional rate of absorption is constant, so absorption decreases the less there is left in the stomach. If a drug is absorbed at a constant rate independent of the amount left to absorb, then it is referred to as having 'zero-order kinetics'.

### Ionization

Absorption of most medicines is dependent on how ionized they are (their  $pK_a$ ) and the acidity at the site of absorption. Drugs with acidic  $pK_a$  values (e.g. aspirin, phenoxymethylpenicillin [penicillin V])

will be mainly non-ionized in the acid stomach and so readily absorbed. Phenobarbital, being a weaker acid, is better absorbed in the more alkaline intestine.

### Neonates

Neonates (especially those who are premature) have reduced gastric acid secretion, so the extent of drug absorption is altered and less predictable.

At birth, drugs with an acidic  $pK_a$  will have decreased absorption. Twenty-four hours after birth, acid is released into the stomach, so increasing the absorption of acidic drugs. Normal adult gastric acid secretions are achieved by about 3 years of age.

Gastric motility is decreased during infancy, thus increasing the absorption of drugs that are absorbed in the stomach. However, drugs absorbed from the intestine will have a decreased or possibly delayed absorption.

### Absorption and $pK_a$ of some drugs in adults and neonates

Drug	Neonatal oral absorption compared with adult	$pK_a$
Ampicillin	Increased	2.7
Penicillin	Increased	2.8
Phenytoin	Decreased	8.3
Paracetamol	Decreased	9.9
Diazepam	Same	3.7

### Rectal

If the enteral route is not available (e.g. vomiting) then the rectum offers an alternative good absorption route. This route is not acceptable to all children and careful dialogue should take place before use of this route. However, if medicines are intended for this route they will be well absorbed provided that they are retained for an adequate length of time which requires them to be placed well up the rectal vault.

### Topical

Although most children will respond similarly to adults with percutaneous administration, extra care and consideration should be taken during infancy and particularly in the first couple of weeks of life and in preterm babies. The immature epidermal barrier, combined with well-hydrated skin and a relatively high surface area:body mass ratio leads to enhanced absorption. Toxicity has been seen with a number of products over the years. Care should be taken with products such as chlorhexidine (especially if in alcohol), povidone–iodine and steroid creams.

# Intramuscular

It may seem strange to say that intramuscular injections should be avoided in childhood when we give intramuscular vitamin K to just about every baby admitted to the neonatal intensive care unit (NICU). However, it is the fact that it acts so slowly from this site of injection (depot effect) that allows it (in this one case) to be so effective – giving several weeks of cover from just the one injection. The lack of muscle and the fact that it is so poorly perfused means that most drugs will just not achieve adequate plasma level concentrations for the route to be effective. The fact that the small muscle mass means that these injections are very painful leads to this route being rarely used in children.

## 1.2 Distribution

The concentration of a drug at various sites of action depends on the drug’s characteristics and those of the tissue. Most drugs are water soluble and will naturally go to organs such as the kidneys, liver, heart and gastrointestinal tract.

At birth, the total body water and extracellular fluid volume are much increased, and thus larger doses of water-soluble drugs are required on a milligram per kilogram (mg/kg) basis to achieve equivalent concentrations to those seen in older children and adults. This has to be balanced against the diminished hepatic and renal function when considering dosing.

	Preterm	Full-term	4–6 months	1 year	>1 year	Adult
Extracellular fluid volume (%)	50	45	40	30	25	25
Total body water (%)	85	75	60	60	60	60
Fat content (%)	3	12	25	30	Variable	18

Distribution is also affected by a decreased protein-binding capacity in newborns, and particularly in preterm newborns, therefore leading to increased levels of the active free drug for highly protein-bound drugs.

- For example, phenytoin is highly protein bound, but, as there is less protein binding in neonates (lower plasma protein levels and lower binding capacity), there is more free phenytoin than in older children and adults. Thus the therapeutic range for phenytoin in neonates is lower than in the rest of the general population because it is the free phenytoin that has the therapeutic action and can cause toxicity
  - Therapeutic range for neonates = 6–15 mg/l
  - Therapeutic range for children and adults = 10–20 mg/l

The reduced protein binding is the result of:

- Low levels of plasma protein, particularly albumin

- Qualitative differences in binding capacity
- Competition with endogenous substances, particularly increased bilirubin after birth

## **Volume of distribution**

Distribution is measured by a theoretical volume in the body called the ‘volume of distribution’. It is the volume that would be necessary to dilute the administered dose to obtain the actual plasma level within the body. The volume will be affected by the following characteristics: body size, body water composition, body fat composition, protein binding, haemodynamics and the drug characteristics. As a rule of thumb drugs that are plasma protein bound will mainly stay in the plasma and thus have a small volume of distribution; highly lipid-soluble drugs (especially in people with a high fat content) will have high volumes of distribution. Water-soluble drugs have increased volumes of distribution in neonates because of the increased total body water content of neonates.

The parameter can change significantly throughout childhood. Plasma albumin levels reach adult levels at approximately 1 year of age.

## **Blood–brain barrier**

The blood–brain barrier in the newborn is functionally incomplete and hence there is an increased penetration of some drugs into the brain.

Transfer across the barrier is determined by the following:

- Lipid solubility
- Degree of ionization

Drugs that are predominantly unionized are more lipid soluble and achieve higher concentrations in the cerebrospinal fluid. It is as a result of this increased uptake that neonates are generally more sensitive to the respiratory depressant effects of opiates than infants and older children.

Some drugs will displace bilirubin from albumin (e.g. sulfonamides), so increasing the risk of kernicterus (encephalopathy due to increased bilirubin in the central nervous system – in at-risk neonates).

## **1.3 Half-life**

Half-life is the time taken for the plasma concentration of a drug to decrease to half of its original value. Thus it follows that less drug will be eliminated in each successive half-life:

- For example, theophylline:
  - if there is initially 250 mg in the body, after one half-life (4 h) 125 mg will remain; after two half-lives (8 h) there will be 62.5 mg left; and so on

When a medicine is first given in a single dose, all the drug is at the absorption site and none is in the plasma. At this point, absorption is maximal and the rate of elimination is zero. As time goes on the rate of absorption decreases (first-order kinetics) and the rate of elimination increases. All the time that the absorption rate is higher than the elimination rate, the plasma level will increase. When the two rates are equal, the concentration in the plasma will be at a maximum. After this point, the elimination rate will be higher and the levels will drop. A drug is said to be at ‘steady state’ after about four to five half-lives. So if multiple dosing is occurring, the plasma levels at any particular point after a dose will always be the same.

## 1.4 Hepatic metabolism

Hepatic metabolism is generally slower at birth compared with adults. However, it increases rapidly during the first few weeks of life, so that in late infancy hepatic metabolism may be more effective than in adults.

The age at which the enzyme processes approach adult values varies with the drug and the metabolic pathway. For drugs such as diazepam, which are extensively metabolized by the liver, the decrease in half-life with age demonstrates this process.

	Preterm babies	Full-term babies	Children
Diazepam half life (h)	38–120	22–46	15–21

The hepatic metabolism process occurs by sulphation, methylation, oxidation, hydroxylation or glucuronidation. Most hepatically metabolized drugs will undergo one or two of these processes.

Processes involving sulphation and methylation are not greatly impaired at birth, whereas those involving oxidation and glucuronidation are. It might be assumed that neonates would be at an increased risk of paracetamol toxicity; however, neonates use the sulphation pathway instead of glucuronidation and are able to deal with paracetamol adequately.

Hydroxylation of drugs is deficient in newborns, particularly in preterm babies, and this is the process that accounts for the huge variation in diazepam half-life as shown in the table above.

Grey-baby syndrome is a rare, but potentially fatal, toxic effect of chloramphenicol in neonates. It is the result of the inability of the liver to glucuronidate the drug effectively in the first couple of weeks of life if correct doses are not given.

It is impossible to predict with any accuracy the possible toxic dose for a neonate and young infant even by applying all the above rules, e.g. neonates unlike adults convert most theophylline to caffeine in the liver. Thus, without dedicated studies we really are only guessing as to what toxic or nontoxic



metabolites are being formed in this age group.

## **First-pass metabolism**

Medication that is absorbed from the gastrointestinal tract goes straight to the liver before entering the systemic circulation. This is useful for some types of medication, which have to go to the liver to be activated (pro-drugs), e.g. enalapril. It is, however, limiting for medications that have to achieve good levels when given orally. Propranolol has a high first-pass metabolism, so quite large doses need to be given to achieve adequate systemic levels. Inhaled budesonide is often said to be relatively free of systemic side effects because the steroid that is deposited in the throat and swallowed is almost entirely eliminated by first-pass metabolism.

## **1.5 Renal excretion**

Drug excretion by the kidneys is mainly dependent on glomerular filtration and active renal tubule secretion. Preterm infants have approximately 15% (or less) of the renal capacity of an adult, term babies have about 30% at birth, but this matures rapidly to about 50% of the adult capacity by the time they are 4–5 weeks old. At 9–12 months of age, the infant's renal capacity is equal to that of an adult.

## **1.6 Other clinical considerations**

Many other factors influence drug handling and may alter an individual's response to a given dose.

## **Pharmacodynamics**

Although pharmacokinetics is significantly different in children (especially infants and neonates) than in adults, the same is not true for the dynamics of most drugs. Generally children respond to medicines in a similar way, but this cannot be assumed and thus any extrapolation of use must be done with great care.

## **Examples**

- Salbutamol is less effective in infancy as the  $\beta_2$  receptors are relatively unresponsive to  $\beta$  agonists
- Caffeine (a xanthine, similar to theophylline) is more effective in neonates than adults due to an enhanced responsiveness of receptors for treating apnoea. Combined with its long half-life and wider therapeutic range it has become the drug of choice for neonatal apnoea against theophylline

## **Genetic variations**

Genetic considerations can lead to altered drug metabolism or altered responses, e.g. glucose 6-phosphate dehydrogenase (G6PD) deficiency, suxamethonium sensitivity, acetylation status.

# G6PD deficiency

This is a commonly inherited enzyme abnormality. It is an X-linked recessive disorder. Male homozygotes show significant drug-related haemolysis, but females only have minor symptoms. Anaemia is the most common presentation.

The following are the main drugs to avoid:

- Dapsone, nitrofurantoin, quinolones (ciprofloxacin, nalidixic acid, ofloxacin, norfloxacin), sulfonamides (co-trimoxazole), quinine, quinidine, chloroquine

# Suxamethonium sensitivity

Some people are extremely sensitive to the muscle relaxant suxamethonium. Serum pseudocholinesterase activity is reduced and the duration of action of the muscle relaxant (usually a few minutes) may be greatly increased, thus leading to apnoea (deaths have been reported). The incidence is about 1 in 2500 of the population.

# Acetylation status

Differences in the metabolism of isoniazid are seen in certain people and inherited as an autosomal recessive trait. People who are ‘slow inactivators’ have reduced activity of acetyltransferase, which is the hepatic enzyme responsible for the metabolism of isoniazid and sulfadimidine (and thus affects phenelzine and hydralazine metabolism). Toxic effects of such drugs may be seen in people who are ‘slow acetylators’.

Slow acetylators are also predisposed to spontaneous and drug-induced systemic lupus erythematosus (SLE).

# Examples of drugs that may induce SLE

Phenytoin	Isoniazid	Procainamide
Penicillin	Chlorpromazine	Tetracyclines
Hydralazine	β Blockers	Lithium
Sulfonamides	Clonidine	Methyldopa

# Liver disease

Toxic substances normally cleared by the liver may accumulate in patients with liver impairment.

- Opioids and benzodiazepines may accumulate and cause central nervous system depression,

thereby causing respiratory depression

- Diuretics (loop and thiazide) may cause hypokalaemia
- Rifampicin, which is excreted via the bile, will accumulate in patients with obstructive jaundice
- Cirrhosis may cause hypoproteinaemia and thus reduce the number of binding sites for highly protein-bound drugs (e.g. phenytoin)
- Clotting factors are reduced in liver impairment, thus increasing the chances of bleeding in patients on warfarin

## Renal disease

- Nephrotoxic drugs will make any renal impairment worse by exacerbating the damage. Drugs that are renally excreted (most water-soluble drugs) will accumulate in renal impairment and the dosing intervals will need to be increased to avoid toxicity

Drugs that cause toxicity in severe renal impairment include:

- Digoxin – cardiac arrhythmias, heart block
- Penicillins/cephalosporins (high-dose) – encephalopathy
- Erythromycin – encephalopathy

Nephrotoxic drugs include:

- Aminoglycosides (gentamicin, amikacin)
- Amphotericin B
- Non-steroidal anti-inflammatory drugs (e.g. diclofenac, indometacin)

## 2. FORMULATION

Medicinal preparations often contain ingredients (i.e. excipients) other than the medicine that is being prescribed. These adjuvants can have a pharmacological effect that needs to be taken into account when looking at medication consumption and assessing possible toxicity.

- Benzyl alcohol and methylparaben can displace bilirubin from albumin-binding sites, leading to exacerbation of jaundice. Benzyl alcohol may also cause a potentially fatal ‘gasping syndrome’
- Propylene glycol is a common solubilizing agent. In excess, it may cause severe toxicity including hyperosmolarity, lactic acidosis, dysrhythmias and hypotension
- Polysorbate 20 and Polysorbate 80, which are used as emulsifying agents, have been associated with renal and hepatic dysfunction as well as hypotension (secondary to hypovolaemia), thrombocytopenia and metabolic acidosis
- Lactose is a common additive, but rarely associated with severe toxicity. It may, however, be important if a child has lactose intolerance
- Sugar and sorbitol are frequently added to liquid preparations for sweetness and occasionally cause problems. Sugar can cause dental caries and sorbitol may cause diarrhoea
- Alcohol is another common ingredient of many liquid pharmaceutical products and the quantity is

often fairly significant. Products such as Phenobarbital BP contain as much as 38% alcohol per 15 mg/5 ml. Equating this to a mg/kg quota, it would not be that unusual to subject a neonate to the equivalent of an adult swallowing one or two glasses of wine

Formulation issues are a fundamental problem in paediatric medicine management. Palatability causes many problems with compliance and it is well demonstrated that taste preferences change with age. Few medicines are made specifically for children and thus products needed in clinical use may not be available in a formulation that is appropriate for young children. This often leads to tablets being crushed and aliquots being given. If this is necessary, the properties of the preparation may change significantly or the dose may be inaccurate, depending on whether the tablet dissolves or disperses and on the release mechanisms built into the tablet originally (e.g. coating or matrix). To put this into some context, a 1-ml aliquot taken from a 50 mg tablet dispersed in 5 ml would be expected to deliver 10 mg. In a study looking at diclofenac dispersible tablets showed that the 1-ml solutions had anywhere between 2 mg and 8 mg (never 10 mg) and that was a 'dispersible' tablet! A pharmacist should be consulted if there is any doubt.

Formulations of the same medicine may differ and give varying effects. This is generally not the case for licensed medicines where a generic medicine will have had to prove that it has a very similar therapeutic effect to the brand leader, although this must still be borne in mind for changes of effect with medicines with narrow therapeutic windows such as anticonvulsants. Even with licensed preparations, different formulations may officially need different dosing, such as the liquid may be more effective than the tablet, e.g. 50 mcg of digoxin liquid is equivalent to 62.5 mcg of the tablet. If medicines are completely unlicensed ('specials' or 'extemporaneously prepared') the situation is very different because there is no licensed standard. Thus not only may a liquid have a completely different bioequivalence to a tablet, but a liquid produced by one manufacturer may contain different excipients and have a different bioequivalence to that produced by another manufacturer. If possible, try to ensure that a child stays on the same product (prescribe, putting the manufacturer, strength and form on the prescription!) to ensure quality continuity of care – this is particularly important when there is transition of care between health-care settings and prescribers.

### 3. PAEDIATRIC DOSING

Pharmacokinetic and pharmacodynamic data are seldom available for children; this is because many medicines are licensed only for adult use and have not undergone specific pre-marketing clinical studies in children. Data on therapeutic dosing for children are often anecdotal and based on case reports or very small population studies. New drugs are usually studied only in adult populations.

Some of the reasons for the lack of medicines licensed in children were the stringent regulations put in place in 1962 after the thalidomide tragedy; these had the effect of discouraging research. However, in recent years European Legislation has changed to encourage more drug companies to seek paediatric licences. This Paediatric Regulation came into force in 2007 and ensures that all new medicines are looked at for their paediatric use potential and if applicable industry has to conduct the paediatric studies. Note that it is not unethical to study medicines in children; it is unethical to use medicines that have not been studied.

The surface area and weight are the only common methods currently available to predict paediatric therapeutic doses from those used for adults.

## Surface area

The surface-area or percentage method for estimating doses is calculated as follows:

$$\frac{\text{Surface area of child (m}^2\text{)}}{1.76 \text{ m}^2} \times 100$$

= Percentage of adult dose

where 1.76 m<sup>2</sup> is the average adult surface area.

Children are often said to tolerate or require larger doses of drugs than adults based on a weight basis, and the percentage method helps to explain this phenomenon. Body water (total and extracellular) is known to equate better with surface area than body weight. It thus seems appropriate to prescribe drugs by surface area if they are distributed through the extracellular fluid volume in particular.

## Weight

$$\frac{\text{Adult dose (mg)}}{70 \text{ kg}} = \text{mg/kg dose}$$

where 70 kg is the average adult weight.

This method will give lower doses than the surface area method. It is far less accurate in clinical terms and is usually inappropriate for accurate therapeutic dosing. However, as it gives lower and thus safer estimates of what the toxic dose may be, it is a more practical and reasonably cautious method for extrapolating toxic doses.

Most paediatric doses given in textbooks are described in small age or weight groups on a milligram per kilogram basis. However, these will often have been originally obtained from surface area data and thus are larger than the adult dose divided by 70.

To estimate the weight of a child (1 year to puberty):

$$\text{Weight (kg)} = 3(\text{age}) + 7$$

There are many algorithms, but this one has reasonable recent data. Always check that the child is 'normal' for age before just accepting the calculated weight.

There are, however, many medications that can be used in children and accuracy of prescribing is

essential because of the vast physical size differences in children (i.e. from 0.5 kg to 120 kg) let alone their changes in kinetics. Children should be regularly weighed so that up-to-date weights can be used for prescribing. However, remember the practicalities of what is to be given to the child. If a child weighs 6.5 kg and requires 2 mg/kg of ranitidine, it would seem wiser to prescribe 15 mg, which is 1 ml of the oral liquid, rather than 13 mg, which equates to 0.867 ml. Some knowledge of the therapeutic range of the drug is required to know when and by how much it is suitable to round doses, and sometimes awkward quantities are required.

These small volumes also create risks in practice for intravenous therapy. A couple of studies have shown that about a quarter of all doses prescribed on an NICU require only a tenth of the content of the preparation kept as stock on the ward with 5% requiring only one-hundredth. Although it is hard to give a 100 times overdose to an adult, it is easy to see how this can happen easily in neonatal practice.

## 4. PRESCRIBING OUTSIDE LICENCE

The unlicensed and off-label (licensed drugs being used outside their licence) use of medicines in children is widespread. It has been accepted by the Royal College of Paediatrics and Child Health (RCPCH) and the Neonatal and Paediatric Pharmacists Group (NPPG) that informed use of such medicines is necessary in paediatric practice when there is no suitable licensed alternative. Those who prescribe for a child should choose the medicine that offers the best prospect for that child, with due regard to cost. Legally, the prescriber is required to take full responsibility for such prescribing, which must be justifiable in accordance with a respectable, responsible body of professional opinion.

The choice of a medicine is not therefore necessarily determined by its licence status, although it should take into account information made available as a consequence of licensing and contained in the summary of product characteristics. This can be of only limited help when the medicine chosen is unlicensed or off-label, and the necessary information to support safe and effective prescribing must be sought elsewhere.

In September 2005 the first *British National Formulary for Children* (BNF-C) was produced and distributed to all doctors and pharmacists by the Department of Health. This was a fundamental move forward in accepting that medicines need to be used outside their licence for children and to try to rationalize and standardize some paediatric medicine management using evidence-based data and expert peer review.

If prescribing outside the licence, remember that the medication supplied has to legally be given with the manufacturer's patient information sheet. This will probably not mention the use for which you are prescribing and may even suggest that it should be avoided in such a condition or age group. This has fundamental implications with compliance and concordance. Leaflets are available on the RCPCH website explaining to children and their carers why this situation may arise, and decreasing the fears that this situation may cause. There are also medicine information leaflets for individual medicines used for specific indications written specifically for parents and carers. These have been developed by the RCPCH, NPPG and the Wellchild charity, and are available at

## 5. DRUG MONITORING

Most drugs have wide therapeutic windows and thus toxicity is unlikely at 'normal doses'. It is usually easy to see a medication effect, e.g. analgesics take away pain. There are, however, certain circumstances when it is important to measure drug levels to ensure that there are adequate levels for effect and/or that the levels are unlikely to cause toxicity.

A drug with a narrow therapeutic window has a narrow range between the drug concentration exhibiting maximum efficacy and that producing minimum toxicity.

Medications that have narrow therapeutic windows are often monitored, because it is hard to predict whether a dose for an individual patient will be clinically effective or will cause toxicity.

Common drugs for therapeutic monitoring	
Phenytoin	
Warfarin	
Carbamazepine	
Gentamicin	
Phenobarbital	
Vancomycin	
Digoxin	
Theophylline	

Indications for monitoring:

- To confirm that levels are not toxic and are at a level that is normally effective (usually checked once steady state has been reached), e.g. gentamicin, vancomycin
- If toxicity is expected
- If external factors may have changed a level (change in renal/hepatic function, change in interacting concomitant medication)
- To check compliance

It is important to know that a drug was at a steady state when a level was measured and whether trough levels or peak levels are important.

### Adverse drug reactions

Whether a drug has a wide or narrow therapeutic index they can all cause adverse drug reactions that can be broken down into different categories:



- Side effects
- Allergic reactions
- Toxic effects (see later)

Probably the greatest worry in children is unexpected adverse drug reactions (ADRs), which are of particular concern in children when using unlicensed and off-label medicines. The variances in kinetics and dynamics means that a side effect may occur that has not been seen in adults. The excipients of the formulation may also give rise to these unexpected ADRs as discussed earlier. Although many side effects are well documented and may even be expected to happen (e.g. increase in heart rate with an infusion of salbutamol), it is suggested that all adverse drug reaction that happen in children are reported using the Yellowcard scheme of the Commission on Human Medicines or Medicines and Healthcare products Regulatory Agency (MHRA) as it is now known, including those using unlicensed and off-label medicines.

## **Drug interactions**

Many situations arise where interactions between different medications are important. Some drugs may just cause the same affects, such as two sedative drugs or medicines with sedation as a side effect will of course lead to an additive effect of sedation. Other drugs may actually interact with each other either in the child's body or before the medicines actually enter the body.

## **Liver interactions**

One drug may alter the metabolism of the other medicine via the effects on liver enzymes. Drugs may either inhibit or induce the liver enzyme systems as follows.

### **Liver induction**

- Will lead to treatment failure of: warfarin, phenytoin, theophylline, oral contraceptive pill
- Caused by: phenytoin, carbamazepine, barbiturates, rifampicin, chronic alcohol consumption, sulfonylureas

### **Liver inhibition**

- Will lead to potentiation of: warfarin, phenytoin, carbamazepine, theophylline, ciclosporin
- Caused by: omeprazole, erythromycin, valproate, isoniazid, cimetidine, sulfonamides, acute alcohol consumption

## **Absorption interactions**

Medication that changes the pH of the stomach or the motility of the stomach may vastly change the absorption of another medication (see [Section 1.1](#)).

Drugs that make the stomach more alkaline include H<sub>2</sub>-receptor antagonists (e.g. ranitidine) and



proton pump inhibitors (e.g. omeprazole).

Drugs that may increase gut transit time include any drugs that may cause diarrhoea, such as many antibiotics but particularly erythromycin.

## Compatibility interactions

When medications are given, always be aware of their interactions before they enter the body. This is particularly important with parenteral medication. Many medications interact to produce non-effective products, toxic products or precipitates.

### Examples of incompatible injections

- Amiodarone: precipitates in the presence of sodium ions
- Fat (in total parenteral nutrition): emulsifies when mixed with heparin
- Erythromycin: is unstable in acidic medium (glucose), so must be made up in sodium chloride
- Gentamicin: is partly inactivated by penicillin, so lines must be flushed between administrations

## 6. INTRAVENOUS MANAGEMENT

The intravenous route offers many advantages to drug administration. By avoiding all the issues of absorption and delivering straight into the blood circulation, you can be fairly sure what dose is circulating and that it is acting quickly. However, unlike most other routes it is finite – once the drug has gone in, there is no way of getting it out if an error has been made.

In children, and especially neonates, medicines often account for a large proportion of their total daily fluid (and electrolyte!) allowance. Although a 1 ml/h infusion in an adult would not be accounted for in their fluid management, the same infusion to a 0.5 kg pre-term infant would equate to almost half their entire circulating fluid volume.

Fluids should be as isotonic with plasma as possible, but children also require more energy than adults and thus the fluids used in children and neonates vary.

**Always review the fluid regimen in light of plasma electrolytes and fluid input/output charts and clinical progress.**

### 6.1 Maintenance fluids

This is the volume required in a 24-h period to maintain normal hydration when there is no significant prior fluid deficit from dehydration and no significant ongoing fluid loss.

#### Type of fluid

Most children should use 0.9% sodium chloride with 5% glucose

Note: use of Hartmann’s solution or 0.9% sodium chloride may be considered as an alternative. Occasionally 0.45% sodium chloride with glucose may be used if sodium levels are dangerously high.

Add potassium chloride 10 mmol/500 ml (20 mmol/l) once U&Es known and urine output established. Children with hypokalaemia may need more (40 mmol/l).

Neonates will require 10% glucose due to their high glucose requirement (usually electrolyte free for the first 48 h of life).

Weight (kg)	Fluid requirement (ml/kg per 24 h)
Day 1 of life	60
Day 2 of life	90
Day 3 of life	120
Day 4 of life and after	120 to 150
>4 weeks of age – 10 kg or less	100
Additionally for each kg up to 20 kg (i.e. 1000 ml+)	50
Additionally for each kg thereafter (i.e. 1500 ml+)	20

Usual maximum of 2500 ml/day in boys and 2000 ml/day in girls.

**Volume of maintenance fluid**

Fluid balance must be monitored and fluids adjusted as needed depending on clinical state (including weight), urine output, environmental factors, plasma and U&E measurements.

**6.2 Monitoring**

Monitor fluid replacement both clinically and biochemically.

Avoid hyponatraemia:

- Hyponatraemia may pre-exist or develop during therapy
- Symptomatic hyponatraemia is a medical emergency

Other electrolyte disturbances may occur and need fluid regimen tailoring based on results:

- Check plasma electrolytes before starting the infusion, except before most cases of elective surgery.

Consider monitoring plasma glucose if glucose-free solutions are used. If postoperative fluids are needed for more than 6–8 h, must send U&Es

- Check plasma electrolytes every 24 h while intravenous fluids are being given. If plasma electrolytes are abnormal, consider rechecking every 4–6 h, but definitely if plasma sodium concentration  $<130$  mmol/l
- Check plasma electrolytes if clinical features suggestive of hyponatraemia develop, including nausea, vomiting, headache, irritability, altered level of consciousness, seizure and apnoea
- Where possible, all children on intravenous fluids should be weighed before the start of therapy and be weighed again each day
- Document accurate fluid balance daily. Assess urine output – oliguria may be due to inadequate fluid, renal failure, obstruction or the effect of antidiuretic hormone

## Rule of 6

Most medicines in adults are infused at a rate of 1 ml/h for the standard dose and then titrated, e.g. morphine 50 mg in 50 ml will normally be started at 1 ml/h, regardless of the size of the adult because adults usually vary in weight only by a magnitude of about twofold (i.e. 50 kg up to 100 kg). Children start at about 0.5 kg for a pre-term baby and also go up to 100 kg – a weight variance of 200-fold, so a standard concentration will not work for all children.

Many continuous infusion medicines are therefore usually worked out using a factor of the weight from an algorithm known as the Rule of 6.

It is worked out with the same principle that 1ml/h of infusion should deliver the ‘usual’ dose:

$(6 \times \text{weight of child in kg})$  mg of drug in 100 ml will deliver 1 mcg/kg per min if run at 1 ml/h

Examples:

$(1 \times \text{kg})$  mg of morphine in 50 ml

1 ml/h = 20 mcg/kg per h

$(3 \times \text{kg})$  mg of midazolam in 50 ml

1 ml/h = 1 mcg/kg per min

## 7. DRUGS IN PREGNANCY

Summary of product characteristics that come with medicines usually indicate whether the medicine can be used (or not) in pregnancy, although most will state that the risk is unknown. This requirement stems from the thalidomide tragedy of the 1960s. It must be remembered that many women are already taking medicines before they know that they are pregnant and others must continue to take medicines for chronic conditions. The specialty of fetal medicine is also growing where high doses of medicines are given to the mother, specifically to treat the unborn child. This is not an area where false

reassurance is appropriate because future litigation is high in this area.

Generally, any effects of medicines will be seen immediately after birth, but some data suggest that this may not be the whole story and long-term effects may also occur, particularly in neurodevelopment.

For medicines that have known teratogenic properties, it is essential that adequate counselling occurs to establish all the risk issues (preferably before they become pregnant).

Neural tube defects are probably the most common teratogenic effect with antiepileptic medication, but warfarin can cause nervous system defects and of course alcohol can cause a multitude of problems under the term 'fetal alcohol syndrome'. However, many factors will affect the fetal response to the teratogen: period of exposure during the pregnancy (first and third trimesters generally being the worst for exposure), dose and genetic factors. Most drugs do cross the placenta and thus will enter the fetus. Some such as insulin are physically too large to cross the barrier, but of course the effects on sugar will still be felt by the unborn baby.

## 8. DRUGS IN BREAST MILK

There is now a great deal of evidence establishing the benefits of breastfeeding for both the mother and the baby. The ability of a drug to pass into the breast milk will depend on its partition coefficient,  $pK_a$ , its plasma and milk protein binding, and selective transport mechanisms. With milk being slightly acidic and fatty, medicines that are acid or protein bound or lipid insoluble are likely to pass into breast milk in low concentrations. Unfortunately, lack of knowledge about drug safety in breastfeeding often causes women to stop breastfeeding or never start in the first place because of their own anxiety or that of the health-care professionals involved in their care.

The *BNF for Children* takes a more pragmatic approach to drugs that are safe in breastfeeding than the licensing manufacturers' information. A majority of medications do pass into breast milk, but most will have little or no effect on an infant at normal therapeutic doses because the dose being delivered to them is subclinical.

It must always be remembered that, even if drugs do enter breast milk, they must still go through the infant's gut to be absorbed and this offers another barrier to many drugs such as omeprazole. The infant's short gastric emptying time also reduces exposure to some drugs.

The frequency and volume of the feeding must also be considered because there will be less exposure to the drug if the infant is receiving supplementary feeds and/or other liquids. Further reassurance can be given to a parent if the medication that is being given has a long-term history of safety in children at therapeutic levels.

Taking all this into consideration, there are very few drugs that are contraindicated in breastfeeding women. The table opposite lists the medicines that are usually seen as a contraindication to breastfeeding. The benefits of breastfeeding usually outweigh the small theoretical risk of harm to the

neonate. This said, we should never become complacent and should look for the evidence and approach newer drugs with more caution.

## Drugs that are contraindicated in breastfeeding

---

Amiodarone  
Androgens  
Antithyroid drugs  
Cancer chemotherapy  
Chloramphenicol  
Dapsone  
Doxepin  
Ergot alkaloids  
Indometacin  
Iodine, Iodides  
Lithium  
Nalidixic acid  
Nitrofurantoin (in G6PD-deficient infants)  
Oestrogens (high dose)  
Radiopharmaceuticals  
Reserpine  
Sulfonamide (in jaundiced or G6PD-deficient infants)  
Tetracyclines  
Vitamins A and D (high dose)

---

G6PD, glucose-6-phosphate dehydrogenase.

## 9. TOXICOLOGY

Each year 40 000 children attend accident and emergency departments (A&Es) with suspected poisonings/accidental ingestion. These incidents fall into three categories:

- Accidental – typically boys in the 1- to 4-year age group
- Intentional – usually teenage girls
- Deliberate – suspected if the signs cannot be explained in any other way

Principles of management include the following:

- Resuscitation if necessary
- Contact a national poisons unit for advice
- Induction of emesis (with ipecacuanha, for example) is no longer indicated
- Consider limiting absorption of poison by:

- Activated charcoal – if ingestion is within 1 hour
- Gastric lavage – if a life-threatening quantity of poison is ingested
- Acid, alkali or corrosive substances should be treated with caution – do not intervene with the above before seeking advice from the poisons unit

## 9.1 Paracetamol

Levels >250 mg/kg are likely to lead to severe liver damage.

### Clinical features

- Nausea and vomiting are the only early symptoms although most patients are asymptomatic
- Right subcostal pain may indicate hepatic necrosis

### Management

- Activated charcoal if ingestion <1 h earlier of 150 mg/kg (75 mg/kg if high risk)
- Measure plasma paracetamol level at 4 hours or as soon as possible thereafter
- Acetylcysteine, a glutathione donor, is almost 100% effective if administered up to 24 hours (ideally 8 hours) post-ingestion in preventing hepatotoxicity and nephrotoxicity
- Be aware of 'high-risk' factors that may require a lower threshold (total paracetamol ingestion as low as 75 mg/kg) for active management. These include conditions that decrease hepatic glutathione stores (e.g. anorexia nervosa, cystic fibrosis, malnourishment) and drugs that induce cytochrome P450 microenzymes (e.g. phenytoin, carbamazepine, rifampicin, phenobarbital)

## 9.2 Iron

Severity of poisoning is related to the amount of elemental iron ingested:

- A 200 mg tablet of ferrous sulphate contains 65 mg elemental iron
- A 300 mg tablet of ferrous gluconate contains 35 mg elemental iron
  - <20 mg/kg – toxicity unlikely
  - >20 mg/kg – toxicity may occur
  - >60 mg/kg – significant iron poisoning

### Clinical features

#### First stage

- Within a few hours:
  - Nausea and vomiting
  - Abdominal pain

- Haematemesis

## Second stage

- 8–16 hours:
  - Apparent recovery

## Third stage

- 16–24 hours:
  - Hypoglycaemia
  - Metabolic acidosis (due to lactic acid)

## Late stage

- Hepatic failure – 2–4 days:

## Management

- Initial treatment depends on the likelihood of toxicity, i.e. was  $>20$  mg/kg ingested?
- Plasma iron level
- Abdominal X-ray:
  - No iron visible but  $>20$  mg/kg ingested: give desferrioxamine orally
  - Iron in stomach: gastric lavage with desferrioxamine in the lavage fluid
  - Iron in intestine: desferrioxamine orally, Picolax orally – a bowel stimulant
- If  $>60$  mg/kg ingested: administer parenteral desferrioxamine

## 9.3 Tricyclic antidepressants

Ingestion of  $>10$  mg/kg of a tricyclic antidepressant is likely to produce significant toxicity, with 20–30 mg/kg potentially being fatal, as a result of sodium channel block leading to cardiac conduction abnormalities.

## Clinical features

- Depressed level of consciousness
- Respiratory depression
- Convulsion
- Arrhythmia
- Hypotension
- Anticholinergic effects:
  - Pupillary dilatation
  - Urinary retention

- Dry mouth

## Management

- Resuscitation
- Activated charcoal within 1 h of ingestion
- ECG monitoring
- Sodium bicarbonate and systemic alkalization:
  - Monitor potassium because sodium bicarbonate can cause hypokalaemia
- All anti-arrhythmics should be avoided especially class Ia agents. Treat convulsions aggressively with benzodiazepines and sodium bicarbonate and, if refractory, with general anaesthesia and supportive care

## 9.4 Aspirin overdose

Mild toxicity follows ingestion of  $>150$  mg/kg with severe toxicity associated with doses  $>500$  mg/kg.

### Clinical features

- In young children, dehydration and tachypnoea
- In older children and adults, tachypnoea and vomiting with progressive lethargy
- Tinnitus and deafness
- Hypoglycaemia or hyperglycaemia can occur

### Three phases

#### Phase 1

- May last up to 12 h
- Salicylates directly stimulate the respiratory centre, resulting in a respiratory alkalosis with a compensatory alkaline urine with bicarbonate sodium and potassium loss

#### Phase 2

- May begin straight away, particularly in a young child, and lasts 12–24 h
- Hypokalaemia with, as a consequence, a paradoxical aciduria despite the alkalosis

#### Phase 3

- After 6–24 h
- Dehydration, hypokalaemia and progressive lactic acidosis, the acidosis now predominating
- Can progress to pulmonary oedema with respiratory failure, disorientation and coma



# Management

- Gastric lavage up to 4 h. Activated charcoal for sustained release preparations. Salicylate level at 6 h plotted on a normogram and repeat every 3–4 h until level has peaked. Levels between 200 and 450 mg/l can be treated by activated charcoal and oral or intravenous rehydration whereas levels >450 mg/l require alkalization
- Alkalization of the urine to aid drug excretion, adequate fluids including bicarbonate, sodium and potassium, with close monitoring of acid–base and electrolytes
- Discuss care with national poisons centre

## 9.5 Lead poisoning

Lead poisoning is uncommon but potentially very serious. It often results from pica (persistent eating of non-nutritive substances, e.g. soil) and is therefore more common in pre-school-age children. Other causes include sucking/ingesting lead paint, lead pipes, discharge from lead batteries and substance abuse of leaded petrol.

Lead intoxication can be divided into acute and chronic effects, and results from its combination with and disruption of vital physiological enzymes.

### Acute intoxication

- Reversible renal Fanconi-like syndrome

### Chronic intoxication

- Failure to thrive
- Abdominal upset: pain/anorexia/vomiting/constipation
- Lead encephalopathy: behavioural and cognitive disturbance, drowsiness, seizures, neuropathies, coma
- Glomerulonephritis and renal failure
- Anaemia – microcytic/hypochromic, basophilic stippling of red cells

A coexisting iron deficiency is common which, first, further exacerbates the anaemia and, second, actually contributes to increased lead absorption. Basophilic stippling is the result of inhibition of pyrimidine 59-nucleotidase and results in accumulation of denatured RNA.

Treatment involves:

- Removing source
- Chelation:
  - Mild – oral D-penicillamine

- Severe – intravenous sodium calcium edetate (EDTA)
- Very severe – intramuscular injections of dimercaprol to increase effect of EDTA

Some US states implement universal screening for elevated lead levels in children.

## 9.6 Carbon monoxide

- Carbon monoxide is a tasteless, odourless, colourless and non-irritant gas
- Carbon monoxide binds to haemoglobin to form carboxyhaemoglobin, which reduces the oxygen-carrying capacity of the blood and shifts the oxygen dissociation curve to the left. The affinity of haemoglobin for carbon monoxide is 250 times greater than that for oxygen
- Endogenous production occurs and maintains a resting carboxyhaemoglobin level of 1–3%
- Smoking increases carboxyhaemoglobin levels. Other sources of raised levels include car exhaust fumes, poorly maintained heating systems and smoke from fires
- Clinical features of carbon monoxide poisoning occur as a result of tissue hypoxia.  $PaO_2$  is normal but the oxygen content of the blood is reduced. Toxicity relates loosely to the maximum carboxyhaemoglobin concentration. Other factors include duration of exposure and age of the patient

### Maximum carboxyhaemoglobin concentration

10%	Not normally associated with symptoms
10–30%	Headache and dyspnoea
60%	Coma, convulsions and death

Neuropsychiatric problems can occur with chronic exposure.

- Treatment of carbon monoxide poisoning is with 100% oxygen, which will reduce the carboxyhaemoglobin concentration. Hyperbaric oxygen is said to reduce the carboxyhaemoglobin level quicker

## 9.7 Button batteries

- Commonly ingested by children
- Systemic toxicity is rare although localized mucosal ulceration is common, possibly leading to gastrointestinal haemorrhage or perforation
- Batteries identified on plain film to be within the oesophagus are to be removed endoscopically
- Patients with batteries within the stomach are to be admitted and re-imaged within 24–48 h. If battery is still in the stomach after 48 h then it must be removed endoscopically
- Batteries distal to the pylorus should not cause problems as long as there is no delay in transit time. It is recommended to monitor progress of the battery with plain films every 48 h to ensure that it

remains intact and has been passed

## 10. FURTHER READING

Briggs GG, Freeman RK, Yaffe SJ (2002). *Drugs in Pregnancy and Lactation*, 6th edn. Philadelphia, PA; Lippincott Williams & Wilkins.

*British National Formulary for Children* (2011). London; BMJ Publishing Group, Royal Pharmaceutical Society and RCPCH Publications.

Conroy S, Nunn T, Tomlin S (2006). Compliance or concordance in children? In; Jacqz-Aigrain E, Choonara I (eds), *Paediatric Clinical Pharmacology*. Lausanne, New York; FontisMedia and Taylor & Francis, 265–273.

Department of Health (2004). *The National Service Framework for Children and Younger People*. London; Department of Health.

Greene SL, Dargan PI, Jones AL (2005). Acute poisoning; understanding 90% of cases in a nutshell. *Postgrad Med J* **81**;204–216.

Jacqz-Aigrain E, Choonara I, eds (2006). *Paediatric Clinical Pharmacology*. Lausanne, York; FontisMedia, and Taylor & Francis.

McIntyre J, Conroy S, Avery A, et al. (2000). Unlicensed and Off-label prescribing of drugs in general practice. *Arch Dis Child* **83**;498–501

Maxwell GW (1989). Paediatric drug dosing. *Drugs* **37**:113–115.

Royal College of Child Health/Neonatal & Paediatric Pharmacists Group (1999). *Medicines for Children*. London: RCCH.

Rylance GM (1988). Prescribing for infants and children. *BMJ* **296**:984–986.

Tomlin S, Cokerill H, Costello I, et al. (2009). *Making Medicines Safer For Children – guidance for the use of unlicensed medicines in paediatric patients*. Guidelines. Connect Medical.

Watson D, Getschman S, Koren G, et al. (1993). Principles of drug prescribing in infants and children: a practical guide. *Drugs* **46**:281–288.

Young YL, Koda Kimble MA (2001). *Applied Therapeutics: The clinical use of drugs*, 6th edn. Philadelphia, PA: Lippincott Williams & Wilkins.

---

# Chapter 6

## Dermatology

*Helen M Goodyear*

---

## CONTENTS

### **1. Structure and function of the skin**

- [1.1 Structure of the skin](#)
- [1.2 Function of the skin](#)
- [1.3 Skin biopsy](#)
- [1.4 Description of skin rashes](#)

### **2. Neonatal skin disorders**

- [2.1 Embryology](#)
- [2.2 Physiological lesions](#)
- [2.3 Differential diagnosis of vesiculopustular lesions](#)
- [2.4 Neonatal erythroderma](#)
- [2.5 Developmental abnormalities](#)
- [2.6 Neonatal lupus erythematosus](#)

### **3. Birthmarks**

- [3.1 Strawberry naevi \(capillary haemangioma\)](#)
- [3.2 Salmon patch \(stork bite\)](#)
- [3.3 Port wine stain \(naevus flammeus\)](#)
- [3.4 Sebaceous naevi](#)
- [3.5 Melanocytic naevi](#)

### **4. Differential diagnosis of an itchy, red rash**

- [4.1 Atopic eczema](#)
- [4.2 Urticaria](#)
- [4.3 Infections and infestations](#)
- [4.4 Psoriasis](#)

## **5. Blistering disorders**

[5.1 Epidermolysis bullosa](#)

[5.2 Drug eruptions](#)

[5.3 Autoimmune blistering disorders](#)

## **6. Erythemas**

[6.1 Erythema multiforme](#)

[6.2 Erythema nodosum](#)

[6.3 Erythema marginatum](#)

[6.4 Erythema migrans](#)

## **7. Photosensitive disorders**

[7.1 Genetic causes of photosensitivity](#)

## **8. Ichthyoses**

[8.1 Inherited ichthyoses](#)

[8.2 Collodion baby](#)

[8.3 Harlequin ichthyosis](#)

## **9. Hair, nails and teeth**

[9.1 Hair](#)

[9.2 Nails](#)

[9.3 Teeth](#)

## **10. Disorders of pigmentation**

[10.1 Causes of hypopigmentation](#)

[10.2 Causes of hyperpigmentation](#)

[10.3 Disorders associated with multiple café-au-lait macules](#)

[10.4 Skin changes associated with tuberous sclerosis](#)

## **11. Miscellaneous disorders**

[11.1 Granuloma annulare](#)

[11.2 Dermatitis artefacta](#)

[11.3 Nappy rash](#)

[11.4 Acne](#)

[11.5 Spitz naevus](#)

[11.6 Keloids](#)

[11.7 Acanthosis nigricans](#)

[11.8 Stings and snake bites](#)

## **12. Further reading**

---

# Dermatology

---

## 1. STRUCTURE AND FUNCTION OF THE SKIN

### 1.1 Structure of the skin

#### Epidermis

##### Four layers

- Stratum corneum – keratinization
- Stratum granulosum
- Stratum spinosum
- Stratum basale

Marked regional variation in thickness of epidermis

##### Cells

- Keratinocytes (95%)
- Merkel cells
- Melanocytes
- Langerhans cells

#### Dermoepidermal junction

A barrier and a filter.

#### Dermis

- 15–20% of body weight
- Variable thickness – 5 mm back, 1 mm eyelids
- Two protein fibres – collagen and elastin
- Supporting matrix/ground substance (proteoglycan (polysaccharide and protein))
- Rich blood supply

##### Cells

- Fibroblasts
- Mast cells
- Macrophages

## Subcutaneous fat

**Epidermal transit time:** 52–75 days. Greatly decreased in hyperproliferative conditions, e.g. psoriasis

**Palmoplantar skin:** extra layer, stratum lucidum, present between stratum granulosum and stratum corneum

**Two types of skin:** glabrous skin on palms and soles and hair-bearing skin

## 1.2 Function of the skin

- **Barrier:** to the inward/outward passage of water and electrolytes
- **Mechanical:** depends on collagen and elastin fibres
- **Immunological:** cytokines, macrophages, lymphocytes and antigen presentation by Langerhans cells
- **UV irradiation protection:** melanin is a barrier in the epidermis, protein barrier in the stratum corneum
- **Temperature regulation:** involves sweat glands and blood vessels in the dermis; heat loss by radiation, convection, conduction and evaporation
- **Sensory:** touch, pain, warmth, cold, itch
- **Respiration:** skin absorbs  $O_2$  and excretes  $CO_2$ , accounting for 1–2% of respiration
- **Endocrine:** vitamin  $D_3$  synthesized in stratum spinosum and stratum basale from pre-vitamin  $D_3$  due to UVB radiation

## 1.3 Skin biopsy

- For uncertain diagnosis, serious skin disorders, histological confirmation of diagnosis before treatment
- Usually a 3- to 4-mm punch biopsy under local anaesthetic. Stitch often not necessary
- Epidermolysis bullosa – needs special shave technique of unaffected rubbed skin

## 1.4 Description of skin rashes

Some dermatological terms:

- **Macule:** a circumscribed area of discoloration
- **Papule:** a small raised area
- **Nodule:** a palpable mass  $>1$  cm in diameter

- **Plaque:** a large disc-shaped lesion
- **Vesicle:** a small blister <0.5 cm in diameter
- **Bulla:** a blister >0.5 cm in diameter
- **Pustule:** a visible accumulation of free pus

## 2. NEONATAL SKIN DISORDERS

### 2.1 Embryology

- **Nails:** form from 8 weeks to 9 weeks onwards
- **Hair:** synthesis from 17 weeks to 19 weeks
- **Keratinization:** of epidermis from 22 weeks to 24 weeks
- **Epidermis:** all layers present from 24 weeks
- **Preterm:** (24–34 weeks) have poor epidermal barrier with thin stratum corneum directly correlating to degree of prematurity; increased skin losses and absorption; within 2 weeks skin is the same as that of term infant
- **Dermis:** is less thick in neonate compared with adult; collagen fibre bundles are smaller, elastin fibres are immature, vascular and neural elements are less well organized

### 2.2 Physiological lesions

- Cutis marmorata
- Physiological scaling
- Vernix caseosa
- Sebaceous gland hyperplasia
- Acrocyanosis (peripheral cyanosis)
- Harlequin colour change
- Sucking blisters
- Milia (large ones = pearls)
- Lanugo hairs in preterm baby

### 2.3 Differential diagnosis of vesiculopustular lesions

#### Transient rashes

- **Miliaria:** blockage of sweat ducts; vesicles (miliaria crystallina) or itchy red papules (miliaria rubra); first 2 weeks
- **Erythema toxicum neonatorum:** in first 48 hours; may recur beyond first month
- **Transient neonatal pustulosis melanosis:** superficial fragile pustules at birth, rupture easily leaving pigmented macule which lasts for up to 3 months



- **Infantile acropustulosis**: presents in first 3 months; recurrent crops of 1- to 4-mm vesicopustules usually on hands and feet; resolves by second to third year
- **Eosinophilic pustular folliculitis**: recurrent crops of papules on scalp, hands and feet; rare, usually in males
- **Neonatal acne**: relatively common, resolves by 3 months

## Infections and infestations

Always take a swab to exclude *Staphylococcus aureus*/streptococcal infection and others in preterm infants or the immunocompromised. Scabies can occur in the first month of life.

## Genetic and naevoid disorders

- **Epidermolysis bullosa**
- **Incontinentia pigmenti**: X-linked dominant, usually lethal in males; vesicular lesions in first 48 hours, verrucous lesions, streaky pigmentation and then atrophic pale lesions; associated with other abnormalities: skeletal, eye, CNS and dentition (SEND)
- **Urticaria pigmentosa**: lesions in first year of life which urticate when rubbed; can be present at birth; systemic involvement is more common if presents >5 years

## 2.4 Neonatal erythroderma

### Causes of neonatal erythroderma

#### Skin disorders

- Seborrhoeic dermatitis
- Atopic eczema
- Psoriasis
- Ichthyosis
- Netherton syndrome

#### Immunological disorders

- Omenn syndrome
- DiGeorge syndrome
- T-cell lymphoma
- Hypogammaglobulinaemia
- Graft-versus-host disease

#### Metabolic/nutritional deficiencies

- Zinc deficiency

- Cystic fibrosis
- Protein malnutrition
- Multiple carboxylase deficiencies
- Amino acid disorders

## 2.5 Developmental abnormalities

- Amniotic bands
- Aplasia cutis congenita: isolated defect commonly on posterior scalp; associations include epidermolysis bullosa, limb defects, spinal dysraphism, trisomy 13, Goltz syndrome and Adams–Oliver syndrome

## 2.6 Neonatal lupus erythematosus

Presents in first few weeks of life. Erythematous scaly rash, typically around the eyes. May be associated with congenital heart block.

## 3. BIRTHMARKS

### 3.1 Strawberry naevi (capillary haemangioma)

- Usually appear in first few weeks of life
- More common in preterm infants
- Precursor is an erythematous/telangiectatic patch  $\pm$  pale halo
- Three phases:
  - Proliferative (6–10 months)
  - Stabilization
  - Spontaneous resolution – pale centre initially
- Complications – ulceration, infection, bleeding, cardiac failure
- Treat if obstructs vital structures (propranolol 2 mg/kg; prednisolone 2–4 mg/kg)
- Often deep component: cavernous haemangioma

**Multiple small diffuse haemangiomas** in infants <3 months of age may be associated with visceral involvement, particularly liver; high mortality if untreated.

**Kasabach–Merritt syndrome:** thrombocytopenia, rapidly enlarging haemangioma, microangiopathic haemolytic anaemia, localized consumption coagulopathy,

**PHACES syndrome:** posterior fossa defects, **haemangiomas** (usually large facial ones), **arterial** anomalies, **cardiac** defects and coarctation of the aorta, **eye** anomalies, **sternal** clefting and/or supraumbilical raphe.

### 3.2 Salmon patch (stork bite)

Nape of neck, upper eyelids, glabella; 10–20% in occipital region persist whereas others resolve spontaneously.

### 3.3 Port wine stain (naevus flammeus)

- Present at birth
- Capillary malformation
- Associations:
  - Sturge–Weber syndrome
  - Klippel–Trenaunay–Weber syndrome
- Persists throughout life
- Can treat with pulse dye laser

### 3.4 Sebaceous naevi

Present at birth; scalp/face; flat/slightly raised and hairless; can undergo neoplastic change after puberty

### 3.5 Melanocytic naevi

Present in 1–2% at birth. Congenital usually >5 mm, acquired <5 mm. Giant melanocytic naevi (bathing trunk naevi) have increased melanoma risk (4–14%). May be associated with neurocutaneous melanosis (EEG abnormalities, raised intracranial pressure, hydrocephalus and space-occupying lesion).

## 4. DIFFERENTIAL DIAGNOSIS OF AN ITCHY, RED RASH

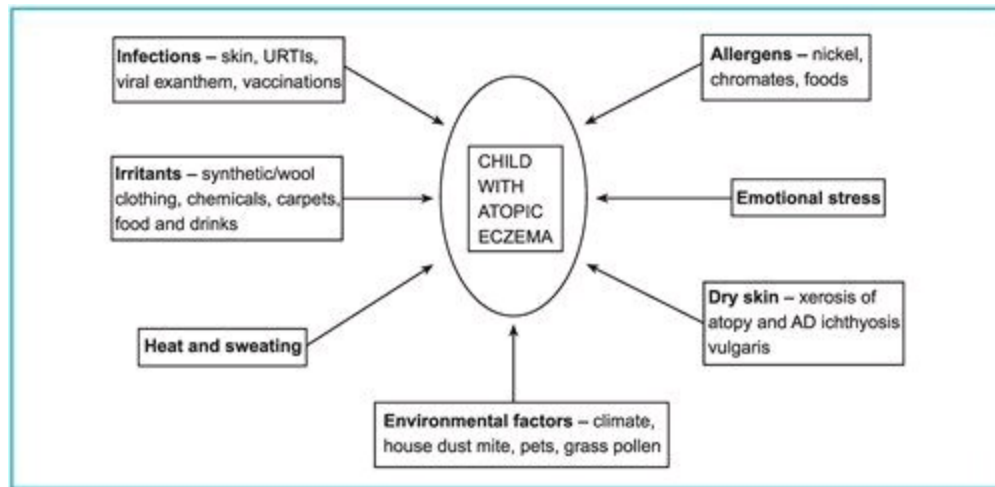
### 4.1 Atopic eczema

Affects 10–20% of children.

**Multifactorial disease** including:

- Genetic factors: 70% of children have positive family history of atopy
- Immunological abnormalities: immunoglobulin E (IgE) dysregulation, skin immune abnormalities – altered cytokine secretion

- Altered pharmacological mechanisms



Exacerbating factors of atopic eczema (URTIs, upper respiratory tract infections; AD, autosomal dominant).

## Features of atopic eczema

- **Age of onset:** usually in first 6 months, around 3 months most common
- **Site:** face/scalp initially, then flexures; extensor aspects may be involved
- **Erythematous macules/papules/plaques/oozing/crust formation**
- **Tendency to secondary infection:** *Staphylococcus aureus*, group A  $\beta$ -haemolytic streptococci, herpes simplex virus (HSV) (eczema herpeticum), warts, molluscum contagiosum
- **Skin colonization** with *S. aureus* in 90%
- **Lichenification:** chronic eczema
- **Resolves:** 50% by 6 years, 90% by 14 years

## Associated conditions

- Ichthyosis vulgaris
- Keratosis pilaris
- Food intolerance and allergy
- Pityriasis alba
- Juvenile plantar dermatosis
- Asthma
- Cataract

## Differential diagnoses

- **Lichen simplex chronicus:** asymmetrical lesion, chronic rubbing and scratching
- **Infantile seborrhoeic dermatitis:** usually in first 3 months, yellow greasy scales on scalp, forehead, napkin area and skin folds, lack of pruritus. Treat with emollients and 1% hydrocortisone if needed (see eczema treatments)

- **Contact dermatitis**
- **Hyper-IgE syndrome (Job syndrome):** IgE >2000 IU/ml, recurrent cutaneous and sinopulmonary infections
- **Wiskott–Aldrich syndrome:** X-linked recessive, thrombocytopenia and recurrent pyogenic infections. Risk of malignancies, non-Hodgkin lymphoma most common

## Management of atopic eczema

### General

- Avoid exacerbating factors
- Cut nails short, file edges
- Wear cotton clothes
- Education for parents and child, demonstrating treatments and giving information to help them self-manage the condition

### Topical treatments

- **Stepwise management** – see NICE guidelines on management of atopic eczema in children aged  $\leq 12$  years
- **Emollients** – bath oil once or twice daily, soap substitute, moisturizer four times daily. Any of the moisturizers can be used as soap substitutes. Aqueous cream should not be used as a leave-on emollient. Use antiseptic bath oils, e.g. Dermol 600, Oilatum Plus, and emollients, e.g. Dermol 500 lotion, Eczmol if recurrent infection
- **Steroid creams/ointments** – weakest strength possible applied twice daily using fingertip unit (FTU) to control the eczema. In general: mild potency 1% hydrocortisone if <2 years; moderate potency if needed, e.g. Eumovate, Betnovate 1 in 4, if >2 years. Never use potent, e.g. Betnovate, or very potent, e.g. Dermovate, in children except in specialized centres. Some evidence that moderate potency three times weekly is as good as mild potency twice daily. Risk of side effects increases with potency and includes skin thinning, irreversible striae and telangiectasia, acne, depigmentation and Cushing syndrome
- **Bandages** – zinc impregnated, e.g. ichthopaste, worn with elasticated bandage such as Coban over the top. Change every 24–48 hours. Useful for chronic limb eczema
- **Wet wraps** – use ready-made vest and leggings with liberal emollient. Make first layer wet with either water or emollient and place second dry layer over the top. Cotton gloves and socks are also available. If itching is a problem then silk suits can be helpful
- **Tacrolimus** (Protopic) 0.03% ointment and **pimecrolimus** (Elidel) works on skin immune system; affecting cytokine release is second-line treatment for atopic eczema that is not improving on conventional treatment. Use twice daily for 3 weeks then once daily. Caution about long-term continuous use due to concerns of cancer risk
- **Antihistamines** – do not use routinely. Use with caution in children < 1 year. One month trial of non-sedating antihistamine for severe atopic eczema or severe itching. Give sedating antihistamine for 7–14 days in acute exacerbations with sleep disturbance
- **Antibiotics** – consider a 10-day course if eczema flares up. Flucloxacillin  $\pm$

phenoxymethylpenicillin or erythromycin. Beware of MRSA (meticillin-resistant *S. aureus*) and resistance to erythromycin in some hospital-acquired *S. aureus* infections

- **Aciclovir** – 1.5 g/m<sup>2</sup> per day intravenously for 5 days if eczema herpeticum (generalized HSV infection of atopic eczema). Oral aciclovir for HSV recurrences. Suspect eczema herpeticum if eczema deteriorates and vesicopustules or punched-out lesions are present
- **Diet** – avoid obvious trigger foods. Give 6- to 8-week trial of hydrolysed protein or amino acid formula to bottle-fed infants with severe eczema aged <6 months. Do not use sheep or goats' milk. Soya protein can be used if >6 months. Involve paediatric dietitian
- **Systemic therapy** – severe eczema unresponsive to above therapies. Therapies include prednisolone (starting around 2 mg/kg to control eczema, then weaning down to lowest alternate-day dose that controls eczema), short-course ciclosporin (up to 5 mg/kg per day) for 3–6 months, monitoring renal and liver function carefully, and azathioprine
- **Alternative remedies** – many patients will use these, e.g. homoeopathy, Chinese herbal medicine. Beware of potent steroid creams in Chinese herbal creams and monitor liver and renal function 3-monthly if taking herbs. Avoid in children <2 years

## 4.2 Urticaria

Transient erythematous/oedematous itchy swellings of the dermis. Lasts from a few minutes to 24 hours. Clears leaving normal skin. Fifty per cent have angio-oedema (swelling of subcutaneous tissues). Histamine is the principal mediator released from mast cells.

### Causes of urticaria

- **Infection**
  - Viral
  - *Streptococcus* sp.
  - *Toxocara canis*
- **Drugs**
  - Penicillin/cephalosporins
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
- **Food**
  - Cows' milk
  - Eggs
  - Nuts
  - Fish
  - Exotic fruits
- **Physical agents**
  - Cholinergic urticaria
  - Cold urticaria
  - Dermatographis
- **Idiopathic (50% cases)**
- **Associated with systemic disease**

## 4.3 Infections and infestations

### Scabies

As a result of the mite *Sarcoptes scabiei humanis*. The mite can survive for 24–36 hours off the human host.

**Variable intensely itchy skin eruption**, about 1 month after infestation, is an immune response to the mite and includes:

- Burrows
- Excoriations
- Eczematization
- Papules
- Vesiculopustular lesions
- Bullae
- Secondary bacterial infection
- Nodules

Burrows common on palms, soles and sides of digits. Examine all family members if scabies is suspected. Treat all family at same time.

### Management of scabies

- Use aqueous-based preparation (alcohol-based preparation will sting), e.g. malathion (Derbac M) and permethrin 5%
- Treat all family members at the same time
- Two applications from the neck downwards at 7-day interval. Get under nails and in skin creases. Reapply after hand washing. Caution if <1 year old, applying for less time depending on age of child
- Apply to lesions on face if present (more common if <1 year)
- Treat any secondary infection with systemic antibiotics
- Treat residual dry skin with emollients
- Wash all clothing, bedlinen and towels at the end of treatment

### Pediculosis

- Usually *Pediculus humanus capitis* (head louse). May get lice on eyelashes and pubic hair
- Occurs in from <10% to 40% of children
- Spread by head-to-head contact
- Pruritus, scratching and excoriation may lead to secondary bacterial infection and cervical lymph nodes

- Look for nits on hairs. Lice visible if recently had a blood meal
- Treat with two applications 7 days apart of malathion-based aqueous lotion or permethrin 5% cream (off-licence use)
- Bug busting with wet combing – evidence varies of effectiveness

## **Viral infections**

Tend to be maculopapular erythematous rashes which may be pruritic. Last from <24 hours to a few weeks. Associated features include cough, runny nose, diarrhoea, vomiting and pyrexia.

## **Tinea**

Erythematous, circular, scaly lesions with clearly defined margin. *Microsporum canis* fluoresces with UV light, *Trichophyton tonsurans* (of human origin, common in inner cities) does not. Take skin scrapings.

## **Impetigo**

Superficially spreading skin infection characterized by yellowish-brown crust. May be bullous. Peaks in late summer and is most common in children <5 years. Causative agent *S. aureus* or group A  $\beta$ -haemolytic streptococci. Treat with oral antibiotics.

## **Staphylococcal scalded skin syndrome**

Caused by exotoxin-producing staphylococci. Localized infection becomes widespread after 24–48 hours. Characteristic signs are fever, skin tenderness, marked erythema, bullae and peeling of the skin. Treat with systemic antibiotics (flucloxacillin) and watch fluid balance.

## **Warts**

Caused by human papillomavirus. Most common on hands and feet (plantar warts/verrucae) but occur at any site. Most resolve spontaneously but can last for several years.

**Treat** with salicylic acid-based wart paint, e.g. Salactol, applying each night and rubbing wart down with an emery board until wart is flat. May need to treat for 3 months or longer. Freezing with liquid nitrogen is effective but often requires multiple treatments at monthly intervals. Poorly tolerated in children <5 years.

## **Perianal warts**

Usually innocently acquired but consider sexual abuse. Only treat if multiple and spreading. Use imiquimod 5% cream three times a week or supervised use of podophyllin 15%. May need surgery.

## **Molluscum contagiosum**



‘Water warts’. Caused by poxvirus. Dome-shaped papules with an umbilicated centre. Spread by autoinoculation. Resolve spontaneously but can last for several years. Treatments tend to be associated with scarring.

Note that both warts and molluscum contagiosum are more common in children who are immunosuppressed and in those with underlying skin disorders such as atopic eczema.

## 4.4 Psoriasis

- **Onset:** <2 years in 2% and at <10 years in 10% of cases of psoriasis. In childhood onset tends to be between 5 and 9 years in girls and 15 and 19 years in boys
- **Increased epidermal turnover time**
- **Relapsing and remitting:** scaly rash, typically affects extensor surfaces and scalp (*Pityriasis amiantacea*)
- **Genetic predisposition:** risk of psoriasis is 10% if a first-degree relative is affected, risk is 50% if both parents are psoriatic; 73% monozygotic and 20% dizygotic twins have concordant disease; HLA-Cw6 (-B13 and -B17) linked to 9–15 times the risk; HLA-B27 associated with psoriatic arthropathy
- **Nail involvement:** pits, onycholysis, subungual hyperkeratosis; may precede onset of skin lesions
- **Arthropathy:** may be severe; higher incidence in patients with nail changes

## Recognized types of psoriasis

- **Common plaque:** chronic psoriasis, psoriasis vulgaris
- **Guttate psoriasis:** (raindrop psoriasis) multiple small lesions on trunk
- **Flexural sites:** intertriginous areas
- **Erythrodermic psoriasis**
- **Pustular psoriasis:** acute generalized form or chronic localized to hands and feet

## Provoking factors

- **Trauma** (Koebner phenomenon)
- **Infection:** streptococcal disease especially in throat in guttate psoriasis; may also play a role in chronic plaque psoriasis
- **Endocrine:** peaks at puberty (and menopause); gets worse in postpartum period
- **Sunlight:** usually beneficial but makes a small number worse
- **Metabolic:** hypocalcaemia, dialysis
- **Drugs:** withdrawal of systemic steroids,  $\beta$  blockers, antimalarials and lithium
- **Psychogenic factors:** stress
- **Human immunodeficiency virus:** psoriasis may appear for the first time or get dramatically worse

## Differential diagnosis

- **Hyperkeratotic eczema**
- **Lichen planus**: flat-topped, purple polygonal papules with white reticulate surface (Wickham striae); oral and nail changes may be present; rare in children; 90% resolve in 12 months
- **Pityriasis rosea**: larger herald patch, smaller lesions in Christmas tree distribution; clears in 6 weeks; linked to human herpesvirus 7
- **Pityriasis lichenoides chronica**: excoriated papules on trunk and limbs in crops; lasts up to a few years

## Management of psoriasis

- **Avoid triggering factors**
- **Treat streptococcal infection**
- **Topical treatment**
  - Emollients
  - Tar-based bath emollients, e.g. Polytar
  - Tar and salicylic acid ointments
  - Vitamin D-derivative creams – calcipotriol (Dovonex) for mild-to-moderate psoriasis (up to 40% of skin area affected)
  - Mild-potency topical steroid creams with tar, e.g. Alphosyl HC for delicate areas, such as the face, flexures, ears, genitals
  - Carefully supervised dithranol preparations, e.g. dithrocream
  - Topical retinoids used but unlicensed
- **Phototherapy**: UVB phototherapy if child is old enough to comply. PUVA is contraindicated in young children
- **Systemic therapy**: severe psoriasis, acute pustular psoriasis, e.g. methotrexate, ciclosporin, acitretin

## 5. BLISTERING DISORDERS

### Causes of blistering disorders

- **Inherited**
  - Epidermolysis bullosa
  - Incontinentia pigmenti
  - Bullous ichthyosiform erythroderma
- **Drugs**
  - Fixed drug eruptions
  - Photosensitivity reactions
  - Sulfonamides
  - Barbiturates
- **Autoimmune**

- Chronic bullous disease of childhood
- Pemphigoid
- Epidermolysis bullosa acquisita
- Dermatitis herpetiformis
- Pemphigus
- **Mechanobullous**
  - Trauma/friction
  - Burns
  - Insect bites/papular urticaria
- **Contact dermatitis**
- **Infection**
  - Bullous impetigo
  - Herpes simplex virus
  - Varicella-zoster
  - Hand, foot and mouth disease
  - Scabies
- **Neonatal disorders**
  - Infantile acropustulosis
  - Miliaria
- **Others**
  - Erythema multiforme
  - Stevens–Johnson syndrome
  - Henoch–Schönlein purpura
  - Porphyria
  - Toxic epidermal necrolysis
  - Hartnup disease
  - Pachyonychia congenita
- **Dermatoses**
  - Eczema
  - Lichen planus

## 5.1 Epidermolysis bullosa (EB)

Heterogeneous condition. Need skin biopsy for definitive diagnosis. First-trimester prenatal diagnosis is possible. Severe types at risk of nutritional deficiencies and anaemia.

There are three broad categories:

- **EB simplex**: mainly autosomal dominant (AD) – defect in basal layer of epidermis affecting keratins 5 and 14. Usually appears when child begins to crawl or walk, with blisters at friction sites, e.g. knees, hands and feet. Hair, teeth and nails not affected
- **Junctional EB**: autosomal recessive (AR) – lethal and non-lethal variants. Mucous membranes can be severely affected and teeth are often abnormal. Laminin-5 defect. Raw denuded areas show

little tendency to heal. Hoarseness as a result of laryngeal involvement

- **Dystrophic EB:** AD and AR – subepidermal blister. Defect in collagen VII production. Lesions heal with scarring. Hair and teeth are normal in dominant form, whereas involvement of mucous membranes, nails, hair and teeth may all be abnormal in recessive form. Web formation between digits leads to a useless fist. May develop squamous carcinoma

## 5.2 Drug eruptions

- **Fixed drug eruptions:** localized brown–purple plaques, may be bullous. Recur at fixed sites when drug is ingested. Hyperpigmentation may persist
- **Hypersensitivity syndrome reactions:** usually 7–28 days after first exposure to drug. Fever, maculopapular/pustular skin lesions, erythema, swelling. Can get nephritis, hepatitis and pneumonitis
- **Severe cutaneous adverse reaction:** erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis
- **Toxic epidermal necrolysis:** bullae, extensive areas of skin necrosis, denuded areas, systemically toxic. May be 1- to 3-day prodrome of high fever, sore throat, conjunctivitis and tender skin. Causative drugs similar to those for Stevens–Johnson syndrome. In toxic epidermal necrolysis there is full-thickness necrosis of epidermis whereas in staphylococcal scalded skin syndrome there is no necrosis and epidermal separation is just beneath the stratum corneum

## 5.3 Autoimmune blistering disorders

All rare. Listed in order of decreasing frequency.

### Chronic bullous dermatosis of childhood

Usually >3 years, mean age 5 years. Tense blisters like a string of pearls usually on abdomen and buttocks. May present as genital blisters/erosions. 40% have mucous membrane involvement. Clears after 3 years. Linear basement membrane IgA.

### Bullous pemphigoid

Can be <12 months. Palm and sole involvement common. Seventy-five per cent have mucous membrane changes. Lasts 2–4 years. Linear basement membrane IgG.

### Dermatitis herpetiformis

Mean age 7 years. Affects buttocks, elbows, back of neck and scalp. Itchy. Fifteen per cent resolve spontaneously. Skin changes can persist up to 18 months after gluten-free diet. IgA in papillary dermis.

## Epidermolysis bullosa acquisita

Mechanobullous picture with blisters localized to areas of trauma. Remits in 2–4 years. Linear basement membrane IgG.

## Pemphigus

Very rare. Flaccid blisters. Nikolsky sign positive (i.e. a blister is induced by rubbing normal-appearing skin). Mucous membrane involvement in vulgaris type, with stomatitis the presenting sign in 50% of cases. Intercellular IgG.

## 6. ERYTHEMAS

### 6.1 Erythema multiforme

Acute self-limiting onset of symmetrical fixed red papules, some of which form target lesions. May blister. Can show Koebner phenomenon. May involve lips, buccal mucosa and tongue.

#### Cause of erythema multiforme

- **Infections**
  - Herpes simplex virus
  - *Mycoplasma* spp.
  - Epstein–Barr virus
  - Chlamydiae
  - Orf
  - Deep fungal infections (histoplasmosis)
- **Drugs**
  - Sulfonamides
  - Penicillin
- **Collagen diseases**
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
- **Underlying malignancy**

## Stevens–Johnson syndrome

Causes as for erythema multiforme but child much more unwell with malaise and a prodromal respiratory illness:

- Severe erosions of at least two mucosal surfaces including eyes, genitalia and internal mucosa (GI and respiratory), with associated swallowing difficulties. Oral mucosa is always involved with haemorrhagic crusting

- Extensive necrosis of lips often with blistering around mouth
- Purulent conjunctivitis
- Variable skin involvement – red macules, bullae, skin necrosis and denudation; Nikolsky sign positive

## 6.2 Erythema nodosum

Nodular, erythematous eruption on extensor aspects of legs, less commonly on thighs and forearms. Regresses to bruises. Lasts 3–6 weeks.

### Causes of erythema nodosum

- **Infections**
  - *Streptococcus* spp.
  - *Salmonella* spp.
  - *Yersinia* spp.
  - *Campylobacter* spp.
  - Tuberculosis
  - Acnes
  - *Chlamydia* spp.
  - Cat-scratch fever
  - Hepatitis B
  - Epstein–Barr virus
  - Mycoses
- **Gut disorders**
  - Ulcerative colitis
  - Crohn disease
- **Malignancy**
  - Leukaemia
  - Lymphoma
- **Drugs**
  - Sulfonamides
  - Oral contraceptive pill

## 6.3 Erythema marginatum

Annular migratory erythema found in 10% of cases of rheumatic fever. Recurrent crops of lesions weekly. Active cardiac disease. Frequently precedes onset of migratory arthritis.

## 6.4 Erythema migrans

Lyme disease due to *Borrelia burgdorferi*. Red papule which develops with annular red ring around it.

## 7. PHOTSENSITIVE DISORDERS

### Causes of photosensitive disorders

- **Idiopathic**
  - Polymorphic light eruption
  - Actinic prurigo
- **Contact dermatitis** due to plants
- **Systemic lupus erythematosus**
  - Photosensitivity rash in 15–30%
- **Drugs**
  - Sulfonamides
  - Thiazides
  - Tetracycline
- **Genetic**

### 7.1 Genetic causes of photosensitivity

#### Phenylketonuria

AD. In addition to photosensitivity, skin changes include:

- Decreased pigmentation
- Eczema
- Fair hair
- Lightly pigmented eyes

#### Xeroderma pigmentosum

AR group of disorders caused by a DNA-repair defect:

- Extreme photosensitivity
- Severe ophthalmological abnormalities
- Skin malignancies in childhood
- Neurological complications in 20%
- Freckling

#### Cockayne syndrome

AR. Cells have increased sensitivity to UV light. Onset of symptoms is in the second year of life:

- Progressive neurological degeneration and growth failure
- Sensorineural hearing loss
- Skeletal abnormalities
- Dental caries
- Pigmentary retinopathy
- Cataracts

## **Trichothiodystrophy**

AR. Hair has low sulphur content. Includes following defects – ‘PIBIDS’:

- **P**hotosensitivity
- **I**chthyosis
- **B**rittle hair
- **I**ntellectual impairment
- **D**ecreased fertility
- **S**hort stature

## **Rothmund–Thomson syndrome**

AR. Characterized by poikiloderma (atrophic pigmented telangiectasia) by end of first year.

- Sparse hair
- Skeletal dysplasia
- Short stature
- Cataracts
- Hypogonadism
- Hypotrophic nails
- Increased risk of osteosarcoma and skin malignancy

## **Bloom syndrome**

AR.

- Growth retardation
- Immunodeficiency (IgA and IgM)
- Telangiectasia
- Pigmentary abnormalities
- Malignancies in third decade – leukaemia, lymphomas

## **Hartnup disease**

AR. Impaired amino acid transport in kidneys and small intestine. Most children asymptomatic:



- Photosensitivity with pellagra-like appearance is first sign
- Can form blisters
- Intermittent cerebellar ataxia
- Psychotic behaviour
- Mild learning disability

## **Porphyrias**

Group of diseases leading to accumulation of haem precursors. 5-Aminolaevulinic acid (ALA) and porphobilinogen (PBG) have no cutaneous manifestations. Elevated porphyrins are associated with either acute photosensitivity or skin fragility with vesiculobullous and erosive lesions.

### **Erythropoietic protoporphyria (EPP)**

Usually AD. Most common porphyria in children:

- Small pitted scars on nose and cheeks
- Burning/stinging sensation on exposed skin
- Photosensitivity less severe in adult life
- Gallstones in childhood
- Excess protoporphyrins in red cells and faeces (urine normal)

### **Congenital erythropoietic porphyria**

AR. Presents at or shortly after birth. Acute episodes become less severe with time, leaving residual scarring, ulceration and marked deformity with sclerodactyly and loss of terminal phalanges.

- Severe photosensitivity
- Red staining of nappy
- Haemolytic anaemia
- Splenomegaly
- Hypertrichosis
- Teeth and bones may be red (fluoresce with UV light)

### **Porphyria cutanea tarda (PCT)**

Familial or provoked by drugs, alcohol or infection.

- Skin fragility leading to vesicles/blisters and erosions
- Hypertrichosis
- Yellow/blue nails and onycholysis
- Systemic manifestations – anorexia, constipation, diarrhoea
- Urine dark brown

## 8. ICHTHYOSSES

Disorders of keratinization, characterized by excessively dry and visibly scaly skin. Hereditary or associated with systemic disease.

### 8.1 Inherited ichthyoses

#### **Ichthyosis vulgaris**

AD. Variable range of expression; may affect in winter months only, affects 1:250. Fine, light scaling. Associated with keratosis pilaris and atopic eczema.

#### **X-linked recessive ichthyosis (XRI, steroid sulphatase deficiency)**

Occurs in 1:2000 boys. Dark-brown scaling affecting limbs and trunk. Gene in Xp22.3 region.

- Cryptorchidism
- Corneal opacities
- Prolonged labour (placental sulphatase deficiency)

#### **Lamellar ichthyoses**

AD and AR. Large, dark, plate-like scales, reptilian appearance.

#### **Bullous ichthyosiform erythroderma**

AD. Erythroderma and severe blistering at birth. Mutations in keratin 1 or 10.

#### **Non-bullous ichthyosiform erythroderma**

AR. Generalized fine scaling and erythroderma.

#### **Associated congenital ichthyoses**

##### **Sjögren–Larsson syndrome**

AR. Fatty alcohol oxidation defect in fibroblasts. Spastic diplegia or tetraplegia, learning disability. Onset of neurological signs at 4–13 months of age.

##### **Refsum disease**

AR. Phytanic acid oxidase defect.

- Retinitis pigmentosa
- Peripheral neuropathy
- Anosmia
- Sensory deafness
- Variable ichthyosis – ichthyosis vulgaris-type appearance

### **Associated steroid sulphatase deficiency**

X-linked recessive ichthyosis can be associated with:

- Kallmann syndrome
- Pyloric stenosis
- Chondroplasia punctata
- Hypogonadism
- Learning disability

### **Multiple sulphatase deficiency**

AR. Lack of arylsulphatase A, B and steroid sulphatase.

- Neurodegenerative disease
- Coarse facies
- Hepatosplenomegaly
- Lumbar kyphosis

### **Trichothiodystrophy syndromes – Tay syndrome and ‘PIBIDS’**

AR. Those with Tay syndrome do not have photosensitivity. Hair has decreased sulphur content.

### **Netherton syndrome**

AR.

- Neonatal erythroderma
- Ichthyosis linearis circumflexa
- Atopy
- Faltering growth
- Recurrent infections
- Trichorrhosis invaginata – hair shaft abnormality

### **Happle syndrome**

X-linked dominant. Conradi–Hunermann syndrome is AD and is now thought not to have cutaneous manifestations.

- Chondroplasia punctata
- Cicatricial alopecia
- Cataracts
- Short stature
- Follicular atrophoderma

## **KID syndrome**

Mode of inheritance uncertain – ? AD or AR.

- **K**eratitis
- **I**chthyosis
- **D**eafness

## **Neutral-lipid storage disease (Chanarin–Dorfman syndrome)**

AR. Fatty changes of the liver, variable neurological and ocular involvement. Multiple lipid vacuoles in monocytes and granulocytes.

## **CHILD syndrome**

Congenital **h**emidysplasia, **i**chthyosiform erythroderma and **l**imb **d**efects.

## **8.2 Collodion baby**

Yellow, shiny, tight film covering skin at birth. Ten per cent have normal skin. Film shed at 1–4 weeks of life. Can persist for 3 months. Biopsy after day 14 is helpful.

### **Disorders presenting as collodion baby include:**

- Gaucher disease
- Lamellar ichthyosis
- Trichothiodystrophy
- Sjögren–Larsson syndrome
- Non-bullous ichthyosiform erythroderma
- Neutral-lipid storage disease
- Chondroplasia punctata
- Ichthyosis vulgaris
- Netherton syndrome

### **Neonatal problems of collodion baby and harlequin ichthyosis (see below)**

- Hypothermia
- Dehydration
- Hypernatraemia
- Cutaneous infection
- Poor sucking

May need up to 250 ml/kg per day fluids. Nurse in high-humidity incubator with up to 1-hourly application of white soft paraffin and liquid paraffin 50:50.

## 8.3 Harlequin ichthyosis

AR. Problems are the same as for collodion babies. Most of the survivors have non-bullous ichthyosiform erythroderma. Need continued high-intensity skin care and high-calorie feeds, otherwise fail to thrive. Use of retinoids (acitretin) is thought to account for increasing survival of these children. Genetic mutation (*ABCA12*) recently identified. *ABCA12* is thought to play a critical role in formation of lamellar granules in the epidermis and the discharge of lipids into the intercellular spaces. This is defective in harlequin ichthyosis and leads to the epidermal barrier defect.

### Features of harlequin ichthyosis at birth:

- Usually preterm
- Erythroderma
- Thick plate-like scales at birth – ‘coat of armour’
- Deep-red fissures
- Ectropion and eclabium (mouth pulled open with eversion of lips)
- Hands and feet have tightly bound digits; tips may be necrotic
- Nose and ears bound down
- Respiratory distress depending upon prematurity and the degree of restriction of chest movement

## 9. HAIR, NAILS AND TEETH

### 9.1 Hair

The hair has cyclical periods of growth throughout life. The three phases are:

- **Anagen:** growth phase
- **Catagen:** intermediate phase
- **Telogen:** resting, usually 3 months before hair being shed

These phases occur randomly so that no one area is depleted of hair. Anagen lasts for variable lengths of time depending on site. Usually >3 years on the scalp.

### Genetic causes of hair loss (diffuse)

- Ectodermal dysplasias – AD/AR. Group of disorders with two or more abnormalities including teeth, nails, sweat glands and other ectodermal structures
- Acrodermatitis enteropathica
- Netherton syndrome
- Cockayne syndrome
- Hair-shaft abnormalities – monilethrix, pili torti, Menkes kinky hair syndrome (X-linked

- recessive – copper transport defect)
- Hartnup disease
- Homocystinuria

## Causes of non-scarring alopecia (hair loss)

- **Telogen effluvium**
- **Trichotillomania**
- **Trauma** from rubbing or traction from pony tails
- **Endocrine causes:** hypothyroidism, hypopituitarism
- **Drugs:** oral contraceptive pill
- **Loose anagen syndrome:** young girls; hair increases in density and thickness as child gets older
- **Nutritional:** malnutrition, iron deficiency, zinc deficiency
- **Alopecia areata**
  - 2% prevalence; usually > 5 years.
  - Family history in 5–25%
  - Associated with autoimmune disorders (thyroiditis, vitiligo) and Down syndrome
  - Scalp is normal in appearance; exclamation-mark hairs are characteristic
  - Outcome unpredictable; most children have small patchy hair loss and outlook is good; the more extensive the disease the worse the prognosis

## Causes of scarring alopecia

- Aplasia cutis congenita
- Systemic lupus erythematosus
- Fungal infection – tinea capitis, kerion
- Incontinenti pigmenti
- *Pachyonychia congenita*
- Epidermolysis bullosa
- Ichthyoses – CHILD syndrome, KID syndrome, syndromes with chondroplasia punctata

## Causes of scalp scaling

- Seborrhoeic dermatitis
- Atopic eczema
- Fungal infection
- Psoriasis
- *Pityriasis amiantacea*
- Histiocytosis

## Excessive hair growth

This is either androgen-independent ‘hypertrichosis’ or androgen-dependent ‘hirsutism’.

## Causes of hypertrichosis

- **Congenital**
  - Hypertrichosis lanuginosa
  - Cornelia de Lange syndrome
  - Rubinstein–Taybi syndrome
  - Hurler syndrome
  - Porphyria – EPP, PCT
- **Endocrine**
  - Hyper-/hypothyroidism
- **Acrodynia** (mercury poisoning)
- **Drugs**
  - Ciclosporin
  - Minoxidil
  - Phenytoin
  - Diazoxide
  - Streptomycin
  - Acetazolamide
- **Head trauma**
- **Dermatomyositis**
- **Focal lesions – Becker naevus**

## Causes of hirsutism

- **Adrenal**
  - Congenital adrenal hyperplasia
  - Cushing syndrome
  - Virilizing adrenal tumours
- **Turner syndrome**
- **Ovarian**
  - Polycystic ovary syndrome
  - Ovarian tumours
  - Gonadal dysgenesis

## 9.2 Nails

Development begins at week 9 of gestation and is complete after week 22. Toenail development lags behind that of fingernails.

### Nail changes – normal variants

- **Koilonychia**: normal variant in early childhood due to thin nail-plate; commonly toenails; also associated with iron deficiency anaemia
- **Superficial longitudinal ridges**: normal variant

- **Beau lines:** transverse depressions; can appear at 1–2 months of age and with any severe illness that affects nail growth
- **Longitudinal pigmented bands:** pigmented bands in dark-skinned children

## Conditions affecting the nails

- **Acute paronychia**
- **Congenital malalignment of the big toe** (triangular shape to nail)
- **Atopic eczema:** pitting, Beau lines, onycholysis
- **Parakeratosis pustulosa:** hyperkeratosis, onycholysis, pitting
- **Psoriasis:** nail pitting, onycholysis, salmon patches of nail-bed
- **Leukonychia:** liver disease, hypoalbuminaemia, hereditary and if punctate found following repetitive minor trauma
- **Twenty nail dystrophy:** many nails affected; spectrum of nail-plate surface abnormalities; may be associated with alopecia areata; regresses spontaneously
- **Lichen planus:** longitudinal ridging, pterygium
- **Nail–patella syndrome:** AD; nail hypoplasia, patella hypoplastic or absent, radial head abnormalities, iliac crest exostosis and nephropathy
- **Epidermolysis bullosa:** may be permanent nail loss
- **Pachyonychia congenita:** AD; severe nail-bed thickening as a result of hyperkeratosis; other features depend on type; include palmar plantar hyperkeratosis, cataracts, alopecia and bullae of palms and soles
- **Ectodermal dysplasias:** variable dystrophic nails depending on type
- **Alopecia areata:** nail pitting
- **Chronic mucocutaneous candidiasis:** nails are yellow–brown and are thickened; recurrence is common because of underlying immune defects
- **Fungal infection**
- **Dystrophy:** CHILD syndrome, congenital erythropoietic porphyria
- **Hypothyroidism:** decreased nail growth, ridging and brittleness
- **Rothmund–Thomson syndrome:** hypotrophic nails
- **Pityriasis rubra pilaris:** half-and-half nail; thickened curved and terminal hyperaemia
- **Incontinentia pigmenti:** nail dystrophy in 40%

## 9.3 Teeth

Always look at the teeth as part of a dermatological examination.

### Conditions affecting the teeth

- **Ectodermal dysplasia:** hypodontia; small, conical, discoloured teeth and caries
- **Epidermolysis bullosa:** dental caries



- **Cockayne syndrome:** dental caries, malocclusion, small mandible so teeth appear large
- **Dyskeratosis congenita:** poorly formed teeth, thin enamel. Degenerative disorder with reticulate skin pigmentation, atrophic nails, leukoplakia and bone marrow failure
- **Congenital syphilis:** Hutchinson teeth (developmental abnormality of upper  $\pm$  lower incisors where teeth are notched/small); mulberry molars (first molars have maldevelopment of cusps and look like mulberries)
- **Congenital erythropoietic porphyria:** teeth may be pink/red and fluoresce with UV light
- **Incontinentia pigmenti:** 80% have dental abnormalities – hypodontia, delayed eruption, malformed crowns
- **Langerhans cell histiocytosis:** premature eruption of teeth
- **Trichothiodystrophy:** enamel hypoplasia, caries

## 10. DISORDERS OF PIGMENTATION

Colour of the skin is the result of melanin produced by melanocytes in the basal layer of the epidermis.

### 10.1 Causes of hypopigmentation

#### Causes of hypopigmentation

- **Nutritional deficiency**
  - Copper
  - Selenium
  - Kwashiorkor
- **Genetic**
  - Oculocutaneous albinism
  - Phenylketonuria
  - Homocystinuria
  - Apert syndrome
  - Piebaldism
  - Waardenburg syndrome
  - Tuberous sclerosis
  - Menkes kinky hair syndrome
  - Epidermolysis bullosa (at sites of bullae)
  - Hypomelanosis of Ito (incontinentia pigmenti achromians of Ito)
- **Autoimmune**
  - Vitiligo
- **Infection**
  - Pityriasis versicolor
  - Vaccination sites
- **Trauma sites**

- **Post-inflammatory**

- Eczema
- Psoriasis

## Chédiak–Higashi syndrome

AR. Incomplete oculocutaneous albinism, photophobia and severe recurrent infections.

## Vitiligo

Total loss of pigment. Often symmetrical. Spontaneous repigmentation uncommon. Associated with autoimmune disorders.

## 10.2 Causes of hyperpigmentation

### Causes of hyperpigmentation

- **Genetic**
  - Incontinentia pigmenti
  - Goltz syndrome (focal dermal hyperplasia)
  - Peutz–Jeghers syndrome
  - Albright syndrome
  - Xeroderma pigmentosum
- **Metabolic**
  - Liver disease
  - Haemochromatosis
  - Wilson disease
  - Porphyrria
  - Congenital erythropoietic porphyria
  - Hepatic cutaneous porphyria
- **Infection**
  - Pityriasis versicolor
- **Drugs**
  - Minocycline
  - Tetracycline
  - AZT (zidovudine)
  - Rifabutin
  - Clofazimine
- **Endocrine**
  - Addison disease
  - Hyperthyroidism
  - Nelson syndrome
  - Cushing syndrome (ectopic ACTH production)

- **Nutritional**
  - Malabsorption
  - Pellagra (sun-exposed sites)
  - Kwashiorkor
- **Post-inflammatory**
  - Insect bites
  - Acne
  - Atopic eczema
  - Lichen simplex chronicus

## Other pigmentary changes

### Niemann–Pick type A

- Grey–brown/yellow–brown discoloration of sun-exposed areas

### Metals

- Silver, bismuth and arsenic
- Slate-grey pigmentation

### Mongolian blue spot

- Blue skin
- Typical site is lower back
- Common in African–Caribbean and Asian babies
- Increased numbers of melanocytes deep in dermis
- Tends to disappear by 4 years of age

## 10.3 Disorders associated with multiple café-au-lait macules

- Neurofibromatosis type I (NFI)
- NFII (minority of patients)
- Piebaldism
- Ataxia telangiectasia
- Multiple endocrine neoplasia
- Russell–Silver syndrome
- McCune–Albright syndrome
- Tuberous sclerosis
- Noonan syndrome
- Bloom syndrome
- Tay syndrome

## 10.4 Skin changes associated with tuberous sclerosis

- Earliest changes are forehead plaques, shagreen patch and hypomelanotic macules. Shagreen patch occurs typically in lumbar region but can be at top of leg
- Facial angiofibromas (adenoma sebaceum): rare <2 years. Present in 85% >5 years
- Periungual fibromas: uncommon in first decade of life

## 11. MISCELLANEOUS DISORDERS

### 11.1 Granuloma annulare

Ring of firm skin-coloured papules. Usually asymptomatic. May follow non-specific trauma in 25%; 50% clear in 2 years; 40% have recurrent eruptions. Link to diabetes mellitus controversial. Always test urine for glucose.

### 11.2 Dermatitis artefacta

Self-inflicted lesions on sites readily accessible to patient's hands. Take a variety of forms including blisters.

### 11.3 Nappy rash

#### Irritant contact dermatitis

- Common
- Due to urine and faeces
- Intertriginous areas characteristically spared
- May be infected with *Candida albicans* (satellite lesions and skinfold involvement)

#### Other causes

- Seborrhoeic dermatitis
- Atopic eczema
- Psoriasis
- Scabies
- Acrodermatitis enteropathica
- Langerhans cell histiocytosis
- Kawasaki disease
- Child abuse
- Blistering disorders

## 11.4 Acne

Affects face and upper trunk. Lesions include comedones, papules, pustules, nodules and cysts. Usually 10–16 years. May get neonatal acne and infantile acne. Investigate for underlying cause if acne appears for the first time between 1 and 7 years.

### Treatment

- Topical – benzoyl peroxide 2.5–10%, topical retinoids, topical antibiotics
- Oral antibiotics – erythromycin, oxytetracycline (not if <12 years) taken twice daily
- Dianette (cyproterone acetate with ethinylestradiol) for females
- Isotretinoin (Roaccutane): vitamin A derivative for severe acne. Causes dry mucous membranes and may cause depression. Counsel and assess for depression before therapy, which is started by a dermatologist only. Teratogenic if taken in pregnancy. Lipid levels and liver function tests should be monitored before treatment and at 1 month

## 11.5 Spitz naevus

Pink/red, sometimes brown in colour. Benign lesion that can be difficult to distinguish from malignant melanoma. Excise if suspicious features, e.g. unusual pigmentation, rapid growth and size >1 cm.

## 11.6 Keloids

Hypertrophic scar extending beyond boundary of original wound. More common in pigmented skin. Intralesional injections of steroid (triamcinolone) may help. Tend to recur if surgically excised.

## 11.7 Acanthosis nigricans

Hyperpigmentation is the earliest feature (‘dirty skin’), preferentially in the flexures. May become hyperkeratotic and warty lesions occur elsewhere on the body. Occurs in families and is associated with obesity, syndromes of insulin resistance, hyper-androgenaemia and hypothyroidism.

## 11.8 Stings and snake bites

### Bee/wasp stings

- **Local effects:** burning, pain, erythema, oedema. Subsides in a few hours
- **Systemic:** usually due to multiple stings. Hypertension, generalized vasodilatation, severe

headache, diarrhoea, vomiting, shock

- **Late-onset reaction:** urticaria, serum sickness-like reaction

## Snake bites

- Depends on type of snake
- Local swelling/necrosis
- Haematological abnormalities including coagulation disturbance and complement depletion
- Treat with compression bandage and immobilization by splinting
- Important to identify venom (in urine, swab and kill snake) so that antivenom can be administered

## 12. FURTHER READING

Ashcroft DM *et al.* (2005). Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomized controlled trials. *BMJ* **330**: 516–22.

Burden AD (1999). Management of psoriasis in childhood. *Clin Exp Dermatol* **24**: 341–5.

Flohr C, Williams HC (2004). Evidence based management of atopic eczema. *Arch Dis Child Educ Pract Ed* **89**: ep35–9.

Higgins E, Du Vivier A (1996). *Skin Disease in Childhood and Adolescence*. Oxford: Blackwell Science.

Irvine AD, Hoeger OH, Yan AC, eds (2011). *Harper's Textbook of Pediatric Dermatology*, 3rd edn. Oxford: Wiley-Blackwell.

Lewis-Jones S, ed (2010). *Paediatric Dermatology*. Oxford: Oxford University Press.

National Institute for Health and Clinical Excellence *Atopic eczema in children: Management of atopic eczema in children from birth up to the age of 12 years*. Available at:  
<http://guidance.nice.org.uk/CG57>

Pediatric Clinics of North America (2000). *Pediatr Dermatol* **47**(4).

---

# Chapter 7

## Emergency Paediatrics

*Serena Cottrell*

---

## CONTENTS

### 1. Introduction

### 2. Out-of-hospital cardiac arrest

- [2.1 Airway opening procedures](#)
- [2.2 Look, listen and feel](#)
- [2.3 Rescue breaths](#)
- [2.4 Checking the circulation](#)
- [2.5 Chest compressions](#)

### 3. In-hospital cardiac arrest

- [3.1 Airway adjuncts](#)
- [3.2 Oxygen](#)
- [3.3 Assessment of rhythm](#)
- [3.4 Treatment of non-shockable rhythms](#)
- [3.5 Treatment of shockable rhythms](#)
- [3.6 Post-resuscitation management](#)
- [3.7 When to stop resuscitation](#)
- [3.8 Resuscitation care plans](#)

### 4. Electrocution injury

- [4.1 Lightning injury](#)
- [4.2 Treatment of electrocution](#)
- [4.3 Myoglobinuria](#)

### 5. Airway

- [5.1 Airway obstruction](#)
- [5.2 Choking](#)

### 5.3 Inadequate airway protection

## **6. Respiratory failure**

### 6.1 Apnoea

### 6.2 Trauma and breathing difficulties

### 6.3 Management of acute severe asthma

### 6.4 Ventilating children with bronchiolitis

### 6.5 Children with pertussis needing admission to the PICU

### 6.6 Cardiac causes of respiratory failure

### 6.7 Treatment of respiratory failure

## **7. Cardiovascular system**

### 7.1 The child with tachycardia

### 7.2 Supraventricular tachycardia

### 7.3 Causes of tachyarrhythmia

### 7.4 Ventricular tachycardia

### 7.5 Causes of bradyarrhythmia

### 7.6 Emergency management of severe heart failure

### 7.7 Recognizing low cardiac output state

### 7.8 Inotropes

### 7.9 The child in shock

## **8. Anaphylaxis**

## **9. Managing the child with severe burns**

### 9.1 Epidemiology

### 9.2 Pathophysiology

### 9.3 Assessment

### 9.4 Indications of an inhalational injury

### 9.5 Assessment of the burn

### 9.6 Treatment

### 9.7 When to transfer to a burns centre

### 9.8 Chemical burns

## **10. Injuries due to severe cold**

### 10.1 Frostbite

### 10.2 Systemic hypothermia

## **11. Severe head injury**

### 11.1 Maintaining an adequate cerebral perfusion pressure

### 11.2 Reducing raised ICP

### 11.3 Complications in intensive care

### 11.4 Imaging



## **12. The convulsing child and the PICU**

[12.1 Pathophysiology](#)

[12.2 Treatment](#)

## **13. Non-traumatic coma**

## **14. Trauma**

[14.1 Life-threatening extremity injuries](#)

[14.2 Gunshot wounds and stabbing](#)

## **15. Drowning**

[15.1 Pathophysiology](#)

[15.2 Treatment](#)

[15.3 Re-warming](#)

[15.4 Prognostic signs](#)

## **16. Further reading**

---

# Emergency Paediatrics

---

## 1. INTRODUCTION

It is vital to have a structured approach when managing a critically ill child. A structured approach enables you to prioritize and stabilize most sick children even when the diagnosis is unknown. Preparation is useful, although not always possible, and good communication is essential both between members of the multidisciplinary team and with families. The structured approach concentrates on identifying and managing the immediate threats to life first: ABCDE, where A for airway, B for breathing, C for circulation, D for disability and E for exposure/environment.

## 2. OUT-OF-HOSPITAL CARDIAC ARREST

Cardiac arrest should be suspected when a patient is found unconscious and not breathing normally and when there are no signs of circulation or palpable pulses.

Traditionally the three Ss approach is taught:

- S safety
- S stimulate
- S shout for assistance

Stimulation may be either verbal or physical, e.g. ‘are you alright?’ to establish responsiveness.

- If there is any risk of cervical spine injury the neck should not be moved while establishing responsiveness

Then the ABCDE approach with basic life support is established.

### 2.1 Airway opening procedures

An obstructed airway results in hypoxia and then cardiac arrest. The airway can be opened by either of two manoeuvres:

- Head tilt with a chin lift (providing that there is no risk of a cervical spine injury)
- Jaw thrust

## 2.2 Look, listen and feel

- **Look** for chest movement
- **Listen** for breath sounds
- **Feel** for the warmth of the breath

## 2.3 Rescue breaths

Agonal/gasping breaths may be present in cardiac arrest so if the child is not breathing normally five rescue breaths should be attempted. The chest should be seen to rise. This can be done with a bag and mask if available.

## 2.4 Checking the circulation

Take no more than 10 seconds to look for signs of circulation. The pulse may also be checked but should not be used as the sole determinant of the need for chest compressions.

Signs of circulation include:

- Any movement
- Coughing
- Normal breathing
- Response to stimulation

The brachial pulse is felt in an infant and the carotid pulse can be felt in a child.

If there are no signs of circulation, no pulse or a slow pulse; in an infant of less than 60 beats/min with poor perfusion or, if you are unsure, start compressions.

## 2.5 Chest compressions

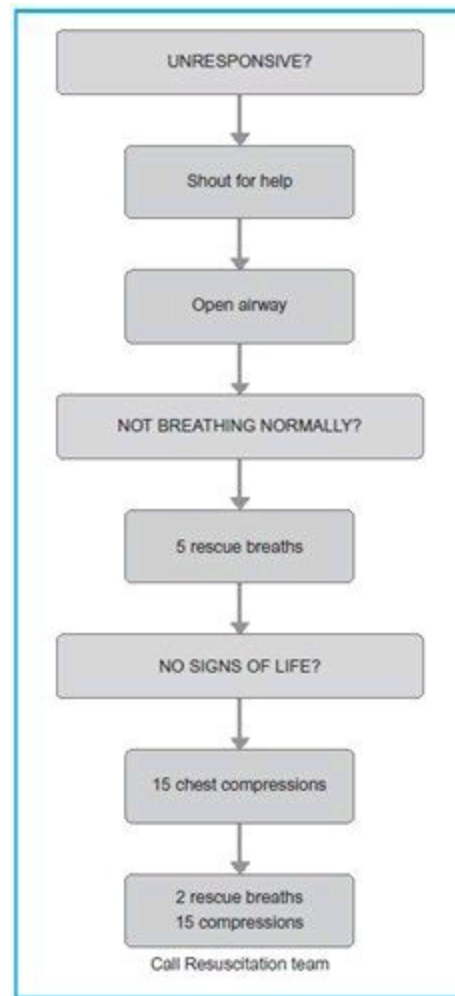
Compressions should be done at a rate of 100–120/min in all ages and should be sufficient to depress the sternum by at least one-third of the depth of the chest.

The ratio is 15 compressions to 2 breaths in both the infant and the child when performed by health professionals. After puberty and in layperson-performed resuscitation, the ratio becomes 30

compressions to 2 breaths. For all children compress over the lower half of the sternum.

## Infant <1 year

- Two fingers for the single rescuer
- Hands encircling the chest, two-thumb technique for two rescuers



Algorithm for basic life support (healthcare professionals with a duty to respond). Reproduced with kind permission of the Resuscitation Council (UK) ([www.resus.org.uk/pages/pbls.pdf](http://www.resus.org.uk/pages/pbls.pdf))

## Child 1 year to puberty

- The heel of one or two hands may be used, depending on the size of the rescuer and the child

## 3. IN-HOSPITAL CARDIAC ARREST

- Safety, stimulate, shout for help
- Initiate basic life support (BLS)
- Call cardiac arrest team

### 3.1 Airway adjuncts

- Oral and nasopharyngeal airways are often underused
- They are particularly useful to aid bagging while awaiting the arrival of a doctor with advanced airway skills or in the pre-arrest child
- **Oral airway**: to find the right size hold the flange of the airway at centre of incisors and the tip should reach to the angle of the mandible
- **Nasal airway**: can be sized by measuring the distance from the tip of the nose to the tragus of the ear

### 3.2 Oxygen

This should be:

- Administered immediately in all arrest scenarios
- Given by facemask or bag and mask with a flow of 15 l/min
- With a reservoir or non-re-breathe bag attached

**Make sure that the arrest team and appropriate senior help are called.**

### 3.3 Assessment of rhythm

Once effective ventilation is achieved with a patent airway and movement of the chest, assess the circulation, including use of monitoring and assessing the rhythm.

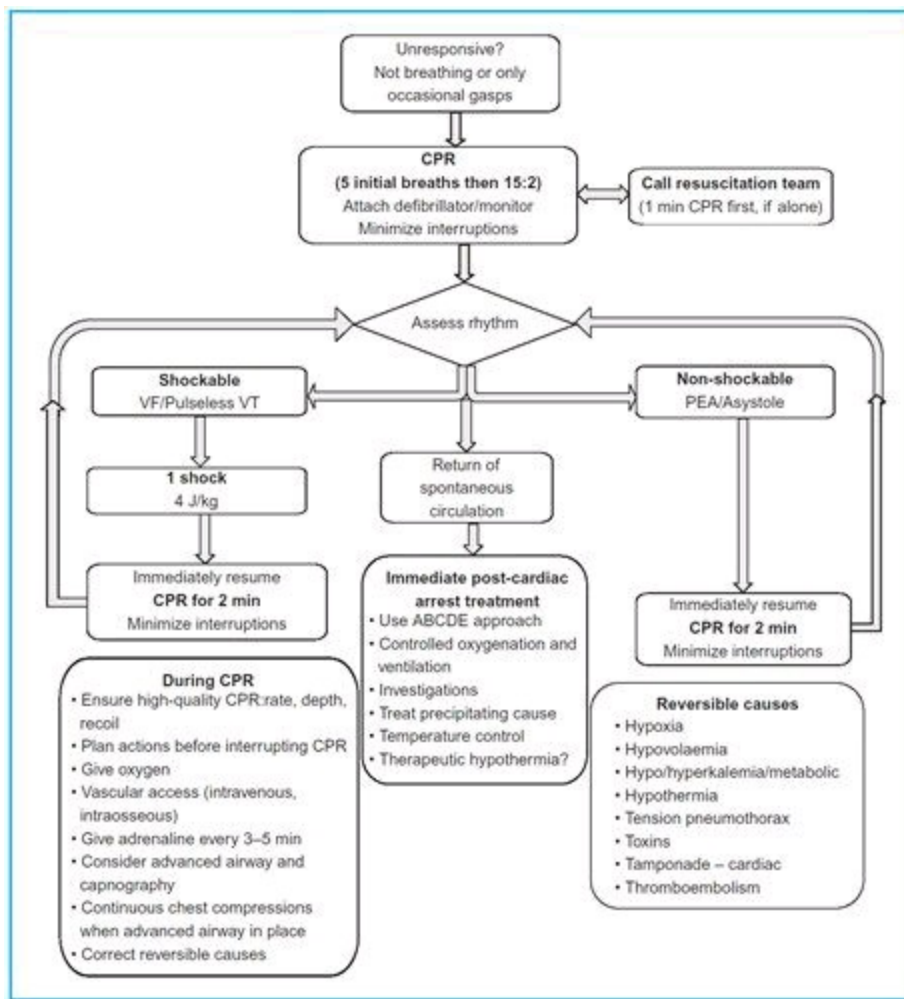
#### **Asystole**

This is the most common arrest rhythm in neonates and children and is usually secondary to hypoxia and acidosis from respiratory failure. It is often preceded by a bradycardia.

- Check the leads are attached correctly
- Increase the gain on the monitor (on some makes of defibrillator this is done automatically)
- Check for signs of life and a pulse (no longer than 10 seconds)

#### **Pulseless electrical activity (PEA)**

There are recognizable complexes on the ECG but no pulse.



Algorithm for advanced management of cardiac arrest. Reproduced with the kind permission of the Resuscitation Council (UK) ([www.resus.org.uk/pages/pals.pdf](http://www.resus.org.uk/pages/pals.pdf))

## Ventricular fibrillation/pulseless ventricular tachycardia

This is an uncommon rhythm in children but can occur in:

- Hypothermia
- Electrocution injury
- Cardiac disease
- Poisoning with tricyclic antidepressants
- Hyperkalaemia

### 3.4 Treatment of non-shockable rhythms

- Interruptions in compressions should be minimized
- Adrenaline 0.1 ml/kg of 1 in 10 000 is given as soon as intravenous access is obtained and then every alternate cycle

### 3.5 Treatment of shockable rhythms

- Interruptions in compressions should be minimized
- Following defibrillation do 2 min of CPR before checking the rhythm
- If the rhythm has altered, do a pulse check
- The shock is asynchronous
- Adrenaline is given after the third shock and then during every alternate cycle (i.e. every 3–5 min)
- Amiodarone (5 mg/kg) is given intravenously after the third shock and then repeated after the fifth shock

### 3.6. Post-resuscitation management

- This usually involves transfer to a paediatric intensive care unit (PICU)
- Regular reassessment should be performed
- Capnography should be used to monitor the carbon dioxide levels
- Pulse oximetry should be used to titrate delivered oxygen once spontaneous circulation has been restored to avoid hyperoxia
- ECG, blood pressure monitoring invasive or non-invasive, temperature, urine output and blood gases should be measured regularly
- Central venous pressure monitoring may also be needed
- Induced hypothermia should be considered

### 3.7. When to stop resuscitation

- The outcome for out-of-hospital cardiac arrest is poor, especially if the rhythm is asystole
- If there is no return of spontaneous circulation after 30 minutes, resuscitation is unlikely to be successful
- In hypothermia, resuscitation should be continued until the child has been warmed
- The decision to stop resuscitation is made by the most senior member of the team

### 3.8. Resuscitation care plans

Children or young people with life-limiting or life-threatening diseases are increasingly being provided with personal resuscitation care plans. Care plans have a number of different titles: advance care plans, emergency care plans, emergency health care plans. These are usually written by the clinician who knows the child best, in partnership with the child, the family and the multidisciplinary team. They usually include a care plan in event of cardiac arrest, a care plan for the event of acute clinical deterioration and a wishes document. The traditional concept of ‘do not attempt cardiopulmonary resuscitation’ (DNACPR/DNAR) is less useful in children and young people, and so a spectrum of options is considered ranging from full resuscitation through to full palliative care. The emphasis is on what to do rather than what not to do, as is traditionally found in DNACPR orders, and gives families options such as considering non-invasive ventilation but not intubation and

full intensive care.

## 4. ELECTROCUTION INJURY

- Severe electrocution injury in children is uncommon
- It can occur with faulty electrical appliances such as living room fires
- If the injury has been obtained out of the domestic environment it is often associated with other injuries such as falls or with the child being thrown into the air
- Being struck by lightning is another cause
- The risk of cardiac arrest is associated with the size of the current, duration of exposure and whether the current is AC (alternating current) or DC (direct current)
- Tetany can occur in the muscles which may make the child cling on to the electrical source, e.g. the bar of an electric fire
- If tetany occurs in the diaphragm and other respiratory muscles, it can lead to a respiratory arrest which continues until the child is disconnected
- May present as a ventricular fibrillation arrest
- Dysrhythmias may occur late
- The child should be examined for entry and exit burns and other injuries should be considered
- The path of the current can be estimated from the site of the entry and exit burns and by assuming that the current will take the path of least resistance from the point of contact to the earth
- Fluid and blood have the least resistance whereas skin and bone have a high resistance
- The damage is caused by heat. Nerves, blood vessels, skin and muscle are damaged the most
- Swelling of tissues, especially muscles, can lead to compartment syndrome and myoglobinuria
- Myoglobinuria occur as a result of massive internal thermal injuries with a relatively small external burn and can lead to renal failure if unrecognized and untreated

### 4.1 Lightning injury

- Large direct current of short duration
- Can depolarize the myocardium and cause immediate asystole

### 4.2 Treatment of electrocution

- Disconnect from source of electrocution
- Immobilize cervical spine
- ABCDE: **a**irway, **b**reathing, **c**irculation, **d**isability and **e**xposure
- A greater fluid requirement is needed because of internal heat injury despite a relatively small external burn

### 4.3 Myoglobinuria



- Occurs after muscle injury such as a crush injury or electrocution
- Myoglobin can be detected in the urine
- Treatment involves maintaining a urine output of more than 2 ml/kg per h by fluid loading and diuretics, using mannitol if required
- Alkalinize the urine by using intravenous sodium bicarbonate to improve the excretion of myoglobin
- Alkalinization of the urine is used to keep a toxin in its ionized form, to reduce the amount of absorption in the renal tubule
- This is called forced alkaline diuresis and is also used for aspirin and phenobarbitone overdose

## 5. AIRWAY

The main aspects of airway that need to be addressed are:

- Obstruction
- Choking
- Failure to protect the airway from aspiration of gastric contents

### 5.1 Airway obstruction

- Obstruction of the airway can occur at all anatomical levels of the respiratory tract from the nose to the small airways. Obstruction of the upper airway is characterized by stridor, which is a high-pitched sound, heard on inspiration, whereas a lower airway obstruction produces an expiratory wheeze
- The upper and lower airways in children are smaller than in adults. Airway resistance is inversely proportional to the radius raised to the power of four. Therefore, halving the radius results in a 16-fold increase in resistance. This means that airway resistance is higher in small children
- Mucosal swelling and secretions are also more likely to obstruct the airway in infants, as the airways are small
- A bubbling or gurgling noise suggests pharyngeal secretions and is common in children with poor pharyngeal tone, as in cerebral palsy
- Poor pharyngeal tone also causes partial obstruction and snoring especially when the child is asleep or post-ictal
- Grunting is more likely to be heard in neonates and is the noise caused by expiration against a partially closed glottis. The lung volume at the end of expiration is almost equal to the closing volume in infants, making atelectasis and areas of collapse common

### Causes of airway obstruction

- Croup/laryngotracheobronchitis (stridor). There may be thick secretions, as in bronchitis, that may, rarely, obstruct the airway

- Epiglottitis (drooling, toxic, quiet stridor)
- Bacterial tracheitis
- Inhaled foreign body
- Asthma (wheeze or silent chest) or bronchiolitis
- Tracheobronchomalacia (prolonged expiratory phase)
- Extrinsic compression: vascular ring, mediastinal tumour
- Facial trauma and burns
- Anaphylaxis
- Angioneurotic oedema
- Retropharyngeal abscess, large tonsils and adenoids
- Diphtheria

## **Treatment of airway obstruction**

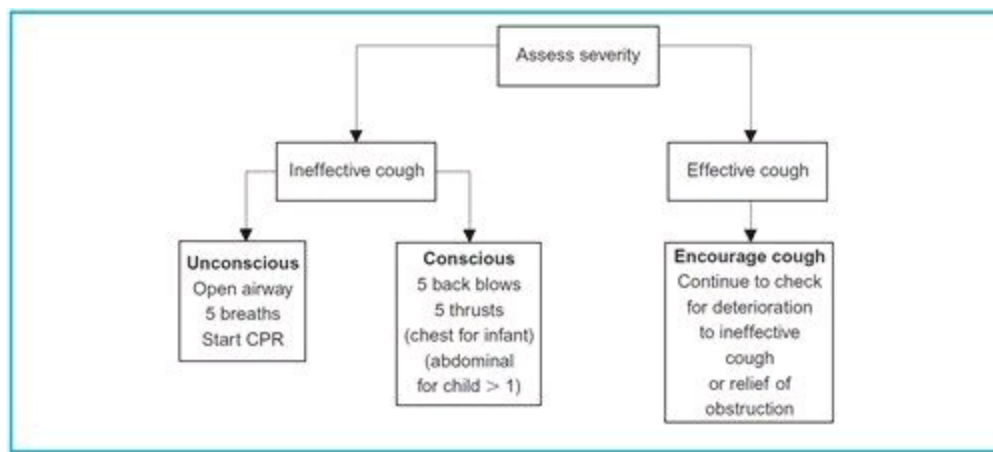
If there is a concern about airway obstruction it is essential to get help from a senior doctor experienced in the management of the airway. It may be necessary to move the child to theatre. Before the arrival of senior help the child should be kept calm, and be left in the position that they find most comfortable, often on the parent's knee. They should be given high-flow oxygen and a saturation monitor should be attached. The saturations in air and high-flow oxygen should be recorded at regular intervals. It is important not to distress the child. Nebulized adrenaline (5 ml of 1:1000) with oxygen through a facemask can be used while awaiting the arrival of experienced help. When experienced help arrives they will intubate using a gas induction anaesthetic of sevoflurane or halothane via an anaesthetic machine. This is usually done in theatre with the ENT surgeon present.

Once the child's airway is secured, oral prednisolone and antibiotics, if a bacterial infection is suspected, can be commenced.

If the obstruction is the result of poor pharyngeal tone a soft nasal airway is useful for both opening the airway and suctioning of secretions.

Airway obstruction can occur with an endotracheal tube in position and is the result of either obstruction distal to the tube or secretions within the lumen of the tube. This presents as desaturation.

## **5.2 Choking**



Paediatric choking treatment algorithm. Reproduced with the kind permission of the Resuscitation Council (UK) ([www.resus.org.uk/pages/pchkalgo.pdf](http://www.resus.org.uk/pages/pchkalgo.pdf))

- A blind finger sweep should not be performed
- The baby is placed along one of the rescuer's arms in the head-down position with the rescuer's hand supporting the baby's jaw, keeping it open in the neutral position
- The rescuer then rests his or her arm along the thigh and delivers five back blows with the heel of the hand
- If the obstruction is not relieved, the baby is turned over and with head down given five chest thrusts using the same landmarks as for cardiac compression
- The back blows and chest thrusts are at a rate of 1/second
- If the infant is too large, place across the rescuer's lap and perform the same technique

## Child choking protocol

- For the choking child, use abdominal thrusts instead of chest thrusts. The rest of the protocol remains the same including the back blows
- The Heimlich manoeuvre can be performed in a child but never in an infant because of the risk of trauma to internal structures. The patient can be standing, sitting, kneeling or lying for the Heimlich manoeuvre

## 5.3 Inadequate airway protection

This is usually the result of decreased consciousness level and has several causes:

- Head injury associated with P on the AVPU scale, only responding to pain or a Glasgow Coma Scale score of 8 and below (A = alert, V = responds to voice, P = responds to pain, U = unconscious)
- Fits
- Metabolic encephalopathy
- Hepatic encephalopathy
- Encephalitis
- Meningitis

- Poisoning and overdoses
- Alcohol intoxication
- Severe sepsis
- Inadequate cardiac output
- Blocked/infected ventriculoperitoneal (VP) shunt
- Diabetic ketoacidosis resulting in cerebral oedema

## **Treatment of inadequately protected airway**

The most immediate treatment is to provide a definitive patent airway. This involves an endotracheal tube placed in the trachea, adequately fixed and attached to a source of ventilatory support.

Adequate preparation and training are essential. Unless the child has arrested it is important to both anaesthetize and give paralysis before attempting intubation. Anaesthetic induction should be performed by an experienced anaesthetist/intensivist or a person trained in airway skills.

If the child is not starved, a rapid sequence induction should be used with cricoid pressure to prevent aspiration of gastric contents.

If there is airway obstruction, it is preferable to use a gas induction using sevoflurane or halothane.

It is important for the paediatrician to recognize airway compromise and to call for appropriate senior help. While awaiting help it is useful to draw up emergency drugs – adrenaline, atropine and suxamethonium – to get out appropriately sized endotracheal tubes, and to know when and how to use basic airway adjuncts such as oral and nasopharyngeal airways.

An endotracheal tube in the right main bronchus, even for a short period of time, can cause right upper lobe collapse. It is therefore important to confirm the position of the endotracheal tube on a chest X-ray soon after placement. It is good practice to write in the notes the size of endotracheal tube used, the length at which it is taped or fixed at the nose or mouth, as well as a comment on the view of the vocal cords at intubation (a grade 1 intubation is where the whole of the cords are viewed) and the degree of space round the tube at the vocal cords.

## **6. RESPIRATORY FAILURE**

Respiratory failure is defined as an inability of physiological compensatory mechanisms to ensure adequate oxygenation and carbon dioxide clearance resulting in either arterial hypoxia or hypercapnia, or both.

The most common causes of respiratory failure are an upper or lower respiratory tract illness; however, disorders of other systems can present with breathing difficulties and should be considered in the differential diagnosis.

## Other causes of respiratory failure

Neuromuscular disease	Muscle weakness	Respiratory failure
Gut disease, e.g. peritonitis	Abdominal distension Pain	Respiratory failure
Cardiac failure	Pulmonary oedema	Tachypnoea
Head injury and fits	Central causes	Reduced respiratory drive
Diabetic ketoacidosis	Metabolic acidosis	Deep sighing respirations
Poisoning		↑ or ↓ respiratory drive

In children with respiratory infections the reduced lung compliance is reflected in recession, which is an indrawing of the ribs and is a useful clinical sign. Recession, however, reduces the efficiency of breathing and makes it harder to retain lung volume.

### 6.1 Apnoea

This is a common sign in neonates and small infants and has a wide differential diagnosis.

- Prematurity
- Bronchiolitis
- Pertussis
- Pneumonia
- Sepsis
- Severe gastro-oesophageal reflux
- Fits
- NAI (non-accidental injury)
- Vascular ring

### 6.2 Trauma and breathing difficulties

Chest injury after trauma can be difficult to differentiate from other causes of respiratory distress. Children's rib cages are much more compliant than those of adults and so rib fractures are far less common. If rib fractures are present it suggests severe chest injury and underlying lung contusion is almost inevitable. If they occur in the absence of a good story of trauma, non-accidental injury should always be considered, although it is important to exclude osteogenesis imperfecta or metabolic bone disease.

If there is a history of trauma, then inhalational injuries and, rarely, a fractured larynx should be considered as well as pneumothorax, tension pneumothorax, massive haemothorax and cardiac tamponade.

Abdominal pain and distension can present with breathing difficulties.

## 6.3 Management of acute severe asthma

The initial treatment of asthma is described in Chapter 22 and is summarized as:

- Oxygen aiming to keep saturations 94–98%
- Nebulized bronchodilators continuously (salbutamol)
- Add in nebulized atrovent
- Hydrocortisone i.v.
- Salbutamol i.v. loading dose for 2–18 year olds 15 µg/kg over 10 min; maximum dose 250 µg
- Salbutamol i.v. up to a maximum of 5 µg/kg per min after an initial loading dose
- Consider magnesium sulphate i.v.

In a child with asthma, ventilation should be avoided if possible but is necessary if the child is either hypoxic or exhausted.

### If child is intubated

- Ketamine is the induction agent of choice as it is a bronchodilator
- Ketamine infusion can be added in
- Manual decompression of the chest on expiration gives an indicator of the severity
- Permissive hypercapnia is a ventilation strategy where the carbon dioxide levels are allowed to rise as long as the pH remains above 7.2
- Finding the ideal level of positive end-expiratory pressure (PEEP) is difficult in a ventilated patient with asthma and is often done by trial and error. Measuring the auto-PEEP can help
- A slow respiratory rate is usually necessary, i.e. <20
- It is important to remember that there is still mortality from asthma and so a respiratory paediatrician should be consulted in any child with asthma severe enough to need admission to the paediatric intensive care unit (PICU)

## 6.4 Ventilating children with bronchiolitis

There are three reasons to ventilate a child with bronchiolitis:

- Apnoea
- Worsening blood gases, usually hypoxia despite maximum oxygen
- Exhaustion

Once a baby is ventilated they:

- need enteral nutrition
- usually need to remain ventilated for at least 4 days or until the basal crepitations have disappeared

Severe bronchiolitis can be confused with pertussis (history, raised lymphocyte count). Prophylactic immunization can be used in children at high risk of respiratory syncytial virus (RSV) bronchiolitis.

## **6.5 Children with pertussis needing admission to the PICU**

- Indications as for bronchiolitis
- Usually babies <2 months of age
- Is associated with a high white cell count
- May have a prolonged stay on the PICU
- Occasionally needs extracorporeal membrane oxygenation (ECMO)

## **6.6 Cardiac causes of respiratory failure**

The pulmonary vascular bed is more muscular in infants and can lead to pulmonary hypertension or pulmonary vasoconstriction. This can lead to right-to-left shunting across a patent foramen ovale, open up the ductus arteriosus or cause shunting across any pre-existing cardiac defects such as an atrial or ventricular septal defect. This results in cyanosis.

Children with cardiac disease with high pulmonary blood flow are more susceptible to pulmonary hypertension. Oxygen is a potent pulmonary vasodilator. It is also important to normalize the carbon dioxide levels and to avoid acidosis. Specific treatments such as inhaled nitric oxide or sildenafil can also be used. Pulmonary hypertension that does not respond to these treatments is called unreactive pulmonary hypertension and is a poor prognostic sign.

## **6.7 Treatment of respiratory failure**

Some form of respiratory support is often needed. This includes:

- Supplementary oxygen with or without an airway
- Non-invasive ventilation
- Conventional ventilation
- Oscillation
- ECMO

## **Airways**

- The oropharyngeal or Guedel airway is poorly tolerated in the conscious patient and may cause vomiting
- The nasopharyngeal airway is better tolerated but may cause haemorrhage from the vascular nasal mucosa

## **Non-invasive ventilation**

- Nasal prong or short-tube continuous positive airway pressure (CPAP) may be an intermediate intervention as is nasal or facemask biphasic positive airway pressure (BIPAP)
- Non-invasive ventilation is particularly useful in children with neuromuscular disorders as an alternative to ventilation, or as part of the weaning process post-extubation
- If there are areas of atelectasis or collapse, recruitment of the lung can be achieved with CPAP or BIPAP, so avoiding the need for intubation

## **Oscillation**

- Oscillation is used as a lung protective strategy to prevent damage to the lungs caused by high pressures and excessive shearing forces
- Oscillation uses a high mean airway pressure to recruit the lung and prevent alveolar collapse

## **ECMO**

- ECMO is a treatment used for reversible conditions where ventilation has become extremely difficult and the pressures required to adequately oxygenate are damaging to the lungs
- For respiratory disorders vein–vein ECMO is used, where both cannulas are inserted into veins
- It can also be used to support the heart either as a bridge to transplantation or if there is a reversible cardiac failure; this requires vein–artery ECMO where both a vein and an artery are cannulated
- ECMO is a very specialist therapy and is performed only in ECMO centres
- A cardiac surgeon inserts the cannulas for ECMO

## **7. CARDIOVASCULAR SYSTEM**

### **7.1 The child with tachycardia**

Tachycardia is one of the most useful clinical signs. There are multiple causes, so having a structured system is helpful. The following system is one of exclusion and is a useful bedside exercise.

There are seven main groups of causes for tachycardia:

- Arrhythmia
- Inadequate cardiac output:



- Preload
- Inotropic
- Afterload
- Tamponade
- Ventilation:
  - Hypoxia
  - Hypercapnia
  - Anaemia
  - Blocked tube
  - Pneumothorax (usually tension)
- Central:
  - Pain
  - Fits
  - Fever
  - Anxiety
- Pulmonary hypertension
- Drugs
- Poor ventricular function

Most of these causes can be excluded on clinical signs or by simple measures such as giving some pain relief. It is then possible to decide whether it is necessary to get a cardiac opinion.

## 7.2 Supraventricular tachycardia

Supraventricular tachycardia (SVT) is the most common tachyarrhythmia dealt with by paediatricians. It can often be difficult to differentiate from a sinus tachycardia. This is because the QRS complex is narrow and regular. The younger the child the more likely SVT will cause cardiovascular instability.

Symptoms include palpitations, heart failure and shock. However, with SVT:

- The onset is sudden as opposed to a gradual increase in rate
- There is no beat-to-beat variation
- The rate does not become slower with a bolus of fluid.
- Rate is usually >220 beats/min in an infant or >180 beats/min in a child
- P waves, if visualized, are negative in leads II, III and AVF

## Treatment of SVT

- ABCDE
- Vagal stimulation
- Diving reflex; iced water on the face or immerse the face in iced water for 5 seconds
- Carotid body massage on one side only
- Valsalva manoeuvre in the older child

# Drug management

Intravenous adenosine must be given quickly and into a large vein followed by a large saline flush – the child must be ECG monitored:

- Start with a bolus of 100 µg/kg
- If unsuccessful after 2 minutes increase the dose to 200 µg/kg
- If unsuccessful after a further 2 minutes increase to 300 µg/kg
- The maximum total dose is:
  - 300 µg/kg if child is <1 month of age
  - 500 µg/kg if child is >1 month – to a maximum of 12 mg single dose
- Side effects are short lived though unpleasant (flushing, nausea, chest tightness, shortness of breath). Some older children describe a feeling of impending doom
- It is important to involve a paediatric cardiologist
- They will consider cardioversion, especially if the child is shocked, or further drug treatment with flecainide, amiodarone, digoxin or β blockers

## Cardioversion

- This should be performed under anaesthesia using a synchronized DC shock
- Initially use 1 J/kg
- Follow with 2 J/kg if unsuccessful
- Hands-free defibrillation is a safe alternative to using the paddles
- A 12-lead ECG is essential to adequately diagnose any change in rhythm.

## 7.3 Causes of tachyarrhythmia

- Re-entrant tachycardia
- Cardiomyopathy
- Post-cardiac surgery
- Drug induced
- Long QT syndrome
- Metabolic disturbances
- Poisoning

## 7.4 Ventricular tachycardia

If the child is haemodynamically stable it is vital to consult a paediatric cardiologist:

- Treat electrolyte disturbances of potassium, calcium and magnesium
- Cardiologists may use amiodarone, often with a loading dose. However, this drug is negatively inotropic and can depress cardiac function

- Use anaesthesia for DC synchronized cardioversion
- Use 1 J/kg, then 2 J/kg

If the child is pulseless follow the ventricular fibrillation protocol.

## 7.5 Causes of bradyarrhythmia

The rate is slow and usually irregular. It is usually a pre-terminal sign.

If there has been a vagal stimulant to the bradycardia use atropine 20 µg/kg i.v. or via interosseous access:

- Pre-terminal event in hypoxia and shock
- Raised intracranial pressure
- Conduction damage post-cardiac surgery
- Congenital heart block
- Myocarditis

## 7.6 Emergency management of severe heart failure

- Assess ABCDE
- Give high-flow oxygen
- Ventilation
- Diuresis
- Offload the heart
- Maximize oxygen-carrying capacity – exclude anaemia
- Inotropes

A child with a severe cardiomyopathy may need a dobutamine infusion. This can be given peripherally through an intravenous cannula. Non-invasive ventilation may also be useful.

The management of heart failure within the context of structural heart defects is discussed in Chapter 1.

## 7.7 Recognizing low cardiac output state

- Tachycardia
- Low urine output or anuria
- Poor capillary refill
- Confusion

Late signs include:

- Hypotension
- Bradycardia
- Confusion can be a late sign
- ST depression on ECG

## 7.8 Inotropes

- An inotrope is used to improve the cardiac output:  
 $\text{Cardiac output} = \text{Heart rate} \times \text{Stroke volume}$
- In the healthy adult the heart has the ability to change its stroke volume dramatically; this occurs during exercise and improves with training
- Neonates, however, have a more fixed stroke volume so need to increase their heart rate to improve the cardiac output
- Once a neonate or child becomes too tachycardic, the heart no longer has time to fill and the cardiac output will reduce
- When a child is in sinus rhythm the atrial kick can provide between 10 and 25% of the cardiac output; if a child goes into atrioventricular block the blood pressure drops
- There is no perfect inotrope as all inotropes have unwanted effects such as increasing the metabolic demands of the heart

The best way to understand which inotrope to use and when is to understand which adrenoreceptor of the sympathetic nervous system each inotrope works on:

- Stimulating  $\beta_1$ -receptors increases both the heart rate and the contractility of the heart
- Stimulating  $\beta_2$ -receptors causes muscle relaxation in the smooth musculature of the airways, causing bronchodilatation, and also relaxes the peripheral vessels, causing a peripheral vasodilatation
- Stimulating  $\alpha$ -receptors causes a peripheral vasoconstriction, increasing the peripheral vascular resistance

Most inotropes stimulate increased production of the enzyme adenylyl cyclase to promote an increase in intracellular calcium, which results in increased contractility of the cardiac muscle.

### Adrenaline

- Works on all the above receptors but its  $\beta_1$ -receptor and  $\alpha$ -receptor effects predominate
- Increases heart rate
- Increases cardiac contractility
- Increases blood pressure by increasing the peripheral vascular resistance

However:

- It makes the heart stiff, i.e. the ventricle is unable to fully relax in diastole
- It greatly increases the metabolic demands of the heart

These effects are also seen with other inotropes.

## **Dopamine**

- Stimulates mainly  $\beta_1$ -receptors at lower doses but at higher doses it has increasing  $\alpha$ -receptor effects
- Increases heart rate
- Increases contractility
- There is probably a low-dose renal effect

However, dopamine is more arrhythmogenic than other inotropes.

## **Dobutamine**

- Stimulates mainly  $\beta_1$ - and  $\beta_2$ -receptors at lower doses but at higher doses it has increasing  $\alpha$ -receptor effects
- Increases heart rate
- Increases contractility of the heart
- Vasodilates at low doses and vasoconstricts at high doses
- Can bronchodilate
- Can be given peripherally

However, like dopamine, it is very arrhythmogenic.

## **Noradrenaline**

- Stimulates mainly  $\alpha$ -receptors, although in large doses it has some  $\beta$ -receptor effects
- Increases blood pressure by increasing the peripheral vascular resistance

## **Milrinone**

- It is a phosphodiesterase inhibitor that works by preventing breakdown of adenylyl cyclase. It is an inotrope that is used mainly with cardiac conditions
- It can be given peripherally
- It has a long half-life (2.5 hours in adults)
- It causes peripheral vasodilatation
- It relaxes the ventricle in diastole (lusitropic action)
- It has an inotropic effect
- It is often termed an inodilator rather than an inotrope

When they are used for more than a few days in large amounts, inotropes become less effective as the receptors down-regulate. When this happens, either the inotrope is changed or steroids are given.

Decreasing the metabolic demands can have an inotrope-like effect. This is seen when a child is ventilated, pain is controlled and pyrexia is treated.

## 7.9 The child in shock

Shock is defined as inadequate perfusion and oxygenation of the tissues.

Causes of shock:

- Cardiogenic, e.g. cardiomyopathy, arrhythmias, myocarditis
- Hypovolaemic, e.g. haemorrhage, burns, gastroenteritis
- Distributive, e.g. anaphylaxis, sepsis
- Dissociative, e.g. severe anaemia, carbon monoxide poisoning
- Obstructive, e.g. tension pneumothorax, cardiac tamponade

Shock is further subdivided into:

- Compensated
- Uncompensated
- Irreversible

The most common causes of shock in children are bleeding, septicaemia and gastroenteritis.

### Septic shock

- One of the most common causes of shock in children is meningococcal disease
- Systemic inflammatory response syndrome is seen, characterized by:
  - Vasodilatation
  - Pyrexia
  - Cascade of inflammatory markers
  - Coagulation disorder
  - Depressed myocardial function

### Spinal shock

- Bradycardia
- Hypotension

## 8. ANAPHYLAXIS

Anaphylaxis can present as respiratory distress with either stridor or wheeze, or as cardiovascular collapse.

## Treatment

- Remove allergen
- Assess ABCDE
- Give high-flow oxygen
- Adrenaline 1:1000 i.m.; <6 years 150 µg (0.15 ml) ; 6–12 years 300 µg (0.3 ml); >12 years 500 µg (0.5 ml) or alternatively 10 µg/kg
- If complete obstruction, obtain a definitive airway
- If partial obstruction:
  - Give nebulized adrenaline 5 ml of 1:1000
  - Give hydrocortisone (<6 months 25 mg; 6 months to 6 years 50 mg; 6–12 years 100 mg; >12 years 200 mg)
  - If wheeze present, give nebulized salbutamol
  - Consider intravenous salbutamol 1–5 µg/kg per min
  - If shock present, give 20 ml/kg fluid bolus, consider adrenaline infusion
  - Chlorpheniramine i.v. (250 µg/kg if <6 months; 6 months to 6 years 2.5 mg; 6–12 years 5 mg; >12 years 10 mg)

## 9. MANAGING THE CHILD WITH SEVERE BURNS

The main issues to consider are:

- Early first-aid measures are important, minimizing the duration of exposure to the heat; tepid water is used
- The airway can deteriorate rapidly and swelling of the airway can make intubation difficult, so early intervention and experienced airway help are necessary
- Shock in the first few hours is unlikely to be the result of the burn injury and other causes of fluid loss, e.g. bleeding, must be considered
- Fluid requirements are high and should be calculated from the time of injury and not from the time of arrival in the accident and emergency department
- Circumferential burns of the chest may restrict breathing so a burns surgeon should be consulted
- Burns are associated with other injuries, e.g. jumping out of windows in house fires or explosions, so consider that the cervical spine, for example, may be injured

### 9.1 Epidemiology

- Burn injuries are very common but the majority are minor
- 70% occur in children <5 years

- Infants and children with learning difficulties are at increased risk
- House fires account for most fatal burn injuries and the cause of death is usually smoke inhalation
- In England and Wales 23 children died in 2001 from burns; in 2007 this had reduced to 18 deaths
- There is a strong link between burns and poverty
- Late infection is a significant cause of morbidity in children with burns injuries

## 9.2 Pathophysiology

- The severity of the burn depends on both the temperature and the time of contact with the burn
- Six hours of contact at 44°C would be needed to cause cellular destruction, whereas at 54°C only 30 seconds of contact is needed to cause cellular destruction

## 9.3 Assessment

- Signs of inadequate breathing include abnormal respiratory rate, abnormal chest movement and cyanosis, which is a late sign
- Reduced consciousness may be the result of other injuries causing hypovolaemia or of a head injury, or it may be secondary to hypoxia
- Child protection issues should be considered

## 9.4 Indications of an inhalational injury

- History of exposure to smoke in a confined space
- Carbonaceous sputum (black sputum)
- Soot deposits around nose or mouth or on clothes

## 9.5 Assessment of the burn

- The severity of the burn is described by the percentage of the total body surface area affected and by the depth of the burn
- The patient's palm and adducted fingers cover a surface area of approximately 1% of the total surface area
- The rule of nines for calculating the percentage burn is not applicable to children and a paediatric chart should be used
- Burns are classified as superficial, partial thickness and full thickness:
  - Superficial burns cause injury only to the epidermis and are red and painful with no blisters
  - Partial-thickness burns are also painful and blistered, and the skin is pink or mottled
  - Full-thickness burns are painless and both the dermis and epidermis are involved and sometimes deeper tissues. The skin is white or charred and feels leathery
- Special areas include the face, hands and feet, perineal burns and circumferential burns, i.e. a burn



that extends round the whole circumference of a limb or trunk, which can act as a tourniquet round the limb or trunk as the burned skin contracts

## 9.6 Treatment

- High-flow oxygen
- Early airway assessment
- Ideally two intravenous cannulas should be placed avoiding burnt areas
- Early and adequate analgesia is important
- Burns of >10% will need extra fluid in addition to their maintenance requirements. The estimated fluid = percentage burn  $\times$  weight (kg)  $\times$  4 given over 24 hours. Half of this is given in the first 8 hours from the burn injury. Urinary catheters are essential in severe burns to assess adequate fluid resuscitation and urine output should be kept at 2 ml/kg per h
- There is a high risk of rapid heat loss following a burn injury so after initial exposure the child should be re-covered and kept warm
- Circumferential burns may need surgical intervention (escharotomies):
  - Escharotomies are needed when the burn injury affects the whole of the dermis and the skin loses its ability to expand as oedema progresses. The burned wound is excised surgically down to the subcutaneous fat
- Carbon monoxide poisoning is discussed in Chapter 5
- Inhalation of carbon monoxide may occur when a child has been in a house fire
- Inhalation of carbon monoxide induces the production of carboxyhaemoglobin which has a much higher affinity for oxygen than normal haemoglobin. Oxygen is therefore not given up to the cells and cellular hypoxia occurs
- The pulse oximeter may show a normal saturation
- The treatment is 100% oxygen or hyperbaric oxygen if very high levels are found

## 9.7 When to transfer to a burns centre

- 10% partial- and/or full-thickness burns
- 5% full-thickness burns
- Burns to special areas: face, hands, feet or perineum
- Any circumferential burn
- Significant inhalational burn (excludes pure carbon monoxide poisoning)
- Chemical, radiation or high-voltage burns

## 9.8 Chemical burns

- Alkali burns are more serious than acid burns because alkalis penetrate more deeply
- If dry powder is present, brush it off before irrigation
- Irrigate with water for 20–30 minutes

## 10. INJURIES DUE TO SEVERE COLD

### 10.1 Frostbite

- Treatment for frostbite should be immediate to reduce the duration of injury unless there is a risk of re-freezing
- Provide warm blankets and a warm drink
- Place the injured part in circulating water at 40°C until pink in colour (periods of 20 minutes are recommended)
- Avoid dry heat
- Give analgesia because re-warming can be very painful
- Cardiac monitoring is required during re-warming

### 10.2 Systemic hypothermia

(See also [Section 15.3](#))

- Core body temperature is below 35°C
- Use special low-registering thermometer
- Decreased level of consciousness is a common sign
- Arrhythmias are common
- Clotting abnormalities occur
- Re-warming can lead to shock, especially if rapid, and should be carried out over the same time period as the initial cooling process
- Cardiac drugs and defibrillation are not usually effective if hypothermia is present, so perform defibrillation only once until the temperature is above 30°C
- The dose interval for adrenaline is doubled between 30°C and 35°C
- Patients should not be pronounced dead until they have been re-warmed to at least 32°C and ideally to above 35°C

## 11. SEVERE HEAD INJURY

The aim of intensive care management in severe head injury is to prevent further brain injury. Therefore, it is important to:

- Maintain good oxygenation
- Avoid hypotension
- Avoid pyrexia
- Avoid hyper- or hypoglycaemia

The head is a closed box once the fontanelle has closed. If there is an expanding lesion within this closed box, such as a bleed or swelling of the brain, the pressure inside the box increases. This is called the Monro–Kellie doctrine.

The compartments in the closed box are:

- Brain
- Cerebrospinal fluid (CSF)
- Arterial blood
- Venous blood

As the brain swells or a bleed increases in size, there is initial compensation. Venous blood and CSF are drained out of the head. Once this has occurred there is a decompensation where a small increase in volume causes a rapid increase in pressure.

The clinical signs of herniation include bradycardia, hypertension and enlarging pupils.

It is important to maintain the blood supply to the brain. This is measured by cerebral perfusion pressure (CPP)

$$\text{CPP} = \text{MAP} - \text{ICP}$$

where MAP = mean arterial blood pressure in mmHg and ICP = intracranial pressure in mmHg.

## 11.1 Maintaining an adequate cerebral perfusion pressure

This requires the blood pressure to be significantly higher than the ICP. The CPP levels for different age groups are a minimum of 40 mmHg in infants and young children and a minimum of 60 mmHg in a teenager or adult.

Often the child needs to be hypertensive to maintain adequate blood supply to the head. A higher than normal blood pressure may be needed to maintain adequate blood supply to the head. This is achieved using noradrenaline as the inotropic support.

This means that a child with a severe head injury will need ventilating, central and arterial access, and a means of measuring the ICP:

- Intracranial bolt
- Ventricular drain
- A device to detect fits, e.g. a cerebral function analysis monitor

## 11.2 Reducing raised ICP

- Keep head central
- Keep head raised 20–30°
- Maintain low to normal CO<sub>2</sub>, aiming for 4.5 kPa
- Maintain high serum sodium levels >140 mmol/l
- Maintain high serum osmolality; give mannitol or hypertonic saline
- Drain CSF from a ventricular drain
- Minimize stimulation to the brain by pain relief and sedation
- Give a paralysing drug
- Provide extra sedation for procedures such as suction
- Avoid seizures

The benefits of either cooling (32–34°C) and/or craniectomy are controversial. It is important to avoid pyrexia.

The outcome following severe head injury is better in children than adults. The initial Glasgow Coma Scale (GCS) at the scene is a useful guide. If it is 8 or less, it is essential to intubate. It is essential to evacuate any expanding bleed as soon as possible; however, speed should not exclude adequate resuscitation.

### 11.3 Complications in intensive care

- Neurogenic diabetes insipidus can occur and, if the urine output is excessive, paired serum and urine osmolalities must be performed and vasopressin given
- Constipation
- Pneumonia
- Pressure sores
- Risk of infection in ventricular drains

### 11.4 Imaging

- Cervical spine injuries cannot be excluded by a normal radiograph or computed tomography (CT), but must be cleared clinically as well
- Regular CT scans of the head are used to monitor progress
- Thoracolumbar spinal radiographs exclude a fracture (if the spine is fractured in one place, there is an increased risk of a second spinal fracture)
- Secondary survey must be documented in the notes. This is a top-to-toe examination for other injuries and is important because smaller non-life-threatening injuries can cause significant morbidity

## 12. THE CONVULSING CHILD AND THE PICU

- Generalized convulsive status epilepticus is defined as a generalized convulsion lasting 30 min or longer or when successive convulsions occur so frequently over a 30-min period that the child does not recover consciousness in between them
- The protocol for the management of status epilepticus is described in Chapter 19
- Mortality still occurs and the rate is 4%. Death may be caused by airway obstruction, aspiration from vomiting, hypoxia, an overdose of medication, cardiac arrhythmias or the underlying disease process
- Complications of prolonged fitting include hyperthermia, arrhythmias, brain damage, hypertension, pulmonary oedema, diffuse intravascular coagulation and myoglobinuria

## 12.1 Pathophysiology

- Convulsions increase the cerebral metabolic rate
- Blood pressure and heart rate increase as a result of a surge in sympathetic activity
- Cerebral arterial regulation is impaired and, as the blood pressure increases, there is increased cerebral blood flow; this is followed by a drop in blood pressure if fits are prolonged and therefore a reduction in cerebral blood flow
- There is an increase in lactate and subsequent cell death and oedema
- The ICP rises
- Calcium and sodium cellular metabolism is impaired

## 12.2 Treatment

- ABCDE and treat hypoglycaemia
- High-flow oxygen
- Follow flow chart in Chapter 19, p. 581)

### **Rapid sequence induction**

This is an anaesthetic procedure undertaken in which there is a risk of aspiration of gastric contents. It involves the following sequence:

- Preoxygenation with 100% oxygen
- Give induction agent (e.g. thiopentone 4 mg/kg or less if the child is hypovolaemic) and muscle relaxant (suxamethonium 2 mg/kg)
- Cricoid pressure is applied by an assistant to occlude the oesophagus
- The child is not bagged during this process
- Intubation
- Assess chest movement to confirm tube position, and listen with a stethoscope in both axillae and over the stomach
- Release cricoid pressure

The child is then taken for a CT scan or to the PICU with full monitoring including saturation monitoring, capnograph, and ECG and blood pressure monitoring

Most children with status epilepticus will stop fitting with these measures. A minority do not and then a thiopental coma is considered.

## **Thiopentone coma**

This usually involves a thiopentone infusion sufficient to achieve burst suppression on the EEG. The coma is continued for 1–3 days. Continuous cerebral function analysis monitoring is needed:

- ICP monitoring may be useful
- Standard neuroprotective measures may be needed if raised ICP is suspected

Complications include:

- Status epilepticus may persist or fits may restart
- Chest infection
- Hypotension secondary to thiopentone
- Renal impairment secondary to thiopentone infusion

Alternatives include high-dose midazolam or high-dose phenobarbitone. A paediatric neurologist must be consulted.

Consider the differential diagnoses:

- Meningoencephalitis
- Pneumococcal meningitis
- Poisoning
- Metabolic disorder
- Electrolyte imbalance
- Trauma
- Pyrexia and infection
- Hypertension
- Non-accidental injury
- Pertussis in a neonate
- Apnoea in a neonate leading to hypoxia

However, a cause is often not found.

## **13. NON-TRAUMATIC COMA**

PICUs are often asked to see these children because there is a concern that they will either hypoventilate or not adequately protect their airway.

In children coma is caused by a diffuse metabolic insult in 95% of cases and by structural lesions in the remaining 5%.

There are many investigations that need to be considered but the following gives the basic essential investigations when the cause of coma is unknown:

- History
- Examination including temperature and pupils
- Haematology
  - Full blood count and film
  - Erythrocyte sedimentation rate
  - Coagulation
- Biochemistry:
  - Blood gas
  - Glucose
  - Urea and electrolytes and creatinine
  - Liver function tests (aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin, albumin)
  - Calcium, phosphate
  - C-reactive protein
  - Serum lactate
  - Ammonia
  - Amino acids (especially raised leucine in maple-syrup urine disease)
  - Creatine kinase
  - Drug levels, e.g. salicylate levels, anticonvulsant levels including thiopental
- Septic screen:
  - Culture and sensitivity; blood, urine, stool, bronchoalveolar lavage (BAL), nasopharyngeal aspirate (NPA)
  - Antibodies – mycoplasma IgG
  - Viral titre – Epstein–Barr virus, herpes virus and common respiratory viruses
  - Virus isolation from NPA and BAL, common respiratory viruses
  - Polymerase chain reaction for meningococci, herpes simplex virus, pneumococci
- Urine:
  - Dipstick
  - Microscopy, culture and sensitivity (MC&S)
  - Toxicology
  - Myoglobin
  - Urine electrolytes
  - Organic acids
  - Ketones
- Chest X-ray
- ECG
- Cranial ultrasound
- EEG

- CT scan

## 14. TRAUMA

### 14.1 Life-threatening extremity injuries

- Crush injuries of the abdomen and pelvis
- Traumatic amputation of an extremity; partial amputation is often more life threatening than complete amputation
- Massive open long-bone fractures

#### **Crush injuries**

- Splinting of the pelvis required
- Embolization of bleeding vessels may be useful
- Trauma to the internal organs is more likely in children than adults after crush injuries

#### **Complete or partial amputation**

- Compression over femoral or brachial artery may help. Use of a tourniquet is now being encouraged in the pre-hospital environment if death from uncontrollable bleeding is likely
- Elevation of the limb
- Advice from a specialist centre

#### **Long-bone fracture**

- Splinting
- Consider vascular injury and compartment syndrome
- Consider tetanus immunization status

### 14.2 Gunshot wounds and stabbing

These are both rare in children but the following tips are useful aide memoires:

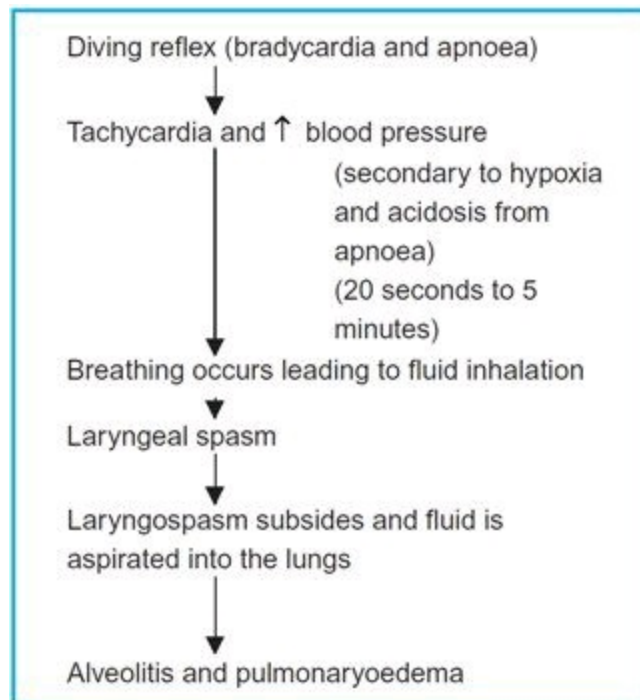
- Bullets usually follow the path of least resistance, so do not assume that the trajectory of the bullet is in a direct line from the entrance to the exit wound
- The entrance wound is often round or oval with a blackened area of burn
- The exit wound is often ragged because of tearing of tissues
- In both stabbing and gunshot wounds it is important to define which structures are likely to have been penetrated



## 15. DROWNING

- 450 000 people die per year worldwide as a result of drowning
- Drowning can occur in even small amounts of water, e.g. a few inches of rainwater in a bucket
- Worldwide, for children <15 years of age, drowning is the most common cause of accidental death
- Most drownings are preventable
- Bradycardia and dysrhythmias are common as a result of the severe hypoxia
- Hypoxia is usually the cause of death

### 15.1 Pathophysiology



Pathophysiology of drowning

### 15.2 Treatment

- ABCDE

Consider:

- Hypothermia
- Hypovolaemia
- Spinal injury
- Electrolyte imbalance
- Other injuries
- Child protection issues
- Contaminated water can lead to infection with unusual organisms

Hypothermia can lead to disorders of coagulation and dysrhythmias and increased risk of infection.

- Remove from the water in a horizontal position to prevent venous pooling and distributive hypovolaemia
- Immobilize the spine
- Early and effective basic life support has been shown to improve outcome
- Secure an airway early and decompress the stomach with a nasogastric tube
- If core temperature  $<30^{\circ}\text{C}$  prevent further cooling and re-warm
- Continue resuscitation until core temperature is at least  $32^{\circ}\text{C}$  and cannot be raised despite active re-warming
- Below  $30^{\circ}\text{C}$  ventricular fibrillation may be refractory. Repeated shocks and inotropes should be delayed until the temperature is above this level, even in circulatory failure

## 15.3 Re-warming

(See also [Section 10.2](#))

### External re-warming

- Remove cold or wet clothes
- Supply warm blankets
- Use a heating blanket
- Use warm air
- Use an infrared radiant heat lamp

### Core re-warming

- Only use warm fluids (warm to  $39^{\circ}\text{C}$ )
- Warm ventilator gases ( $42^{\circ}\text{C}$ )
- Warm peritoneal dialysis fluids at  $42^{\circ}\text{C}$
- Gastric or bladder lavage with 0.9% saline at  $42^{\circ}\text{C}$
- Pleural or pericardial lavage

### Extracorporeal blood warming

- External re-warming is appropriate for temperatures  $>30^{\circ}\text{C}$
- During re-warming vasodilatation occurs, producing a relative hypovolaemia, often requiring fluid boluses
- Re-warming also increases the metabolic demands on the heart so myocardial dysfunction may become apparent on re-warming. Inotropes may be needed once the temperature is above  $30^{\circ}\text{C}$

## 15.4 Prognostic signs

Signs associated with a poor prognosis:

- Immersion for >10 min
- If no respiratory effort has occurred after 40 min of full CPR, the chances of survival are small; however, caveats to this are immersion in very cold water, a history of medication or alcohol intake
- It is unlikely for water in the UK to ever be cold enough to be neuroprotective
- Persisting coma
- pH <7.1 despite treatment
- $PO_2$  <8 kPa despite treatment

Signs associated with a good prognosis:

- If respiratory effort occurs within 3 min of starting CPR, the prognosis is good
- Provision of basic life support at the scene

Respiratory compromise may occur several hours after the drowning episode.

## 16. FURTHER READING

Advanced Life Support Group (2011). *Advanced Paediatric Life Support*, 5th edn. London: BMJ Books, Wiley-Blackwell.

Pearson G (2002). *Handbook of Paediatric Intensive Care*. London: Saunders.

Resuscitation Council (2010). *Resuscitation Guidelines*. London: Resuscitation Council.

Resuscitation Council (2011). *Emergency Paediatric Life Support*, 3rd edn. London: Resuscitation Council.

Shann F, Henning H (2005). *Paediatric Intensive Care Guidelines*, 12th edn. Collective Pty Ltd.

South Central Strategic Health Authority (2010). *Advance Care Planning (ACP): ACP, Policy and Staff Guide*. Available at: [www.southcentral.nhs.uk/what-we-are-doing/end-of-life-care/childrens-advance-care-plan](http://www.southcentral.nhs.uk/what-we-are-doing/end-of-life-care/childrens-advance-care-plan) (accessed November 2011).

---

# Chapter 8

## Endocrinology and Diabetes

*Heather Mitchell and Vasanta Nanduri*

---

## CONTENTS

### **1. Hormones**

- [1.1 Introduction](#)
- [1.2 Hormone physiology](#)
- [1.3 Hormone–receptor interactions](#)
- [1.4 Second messengers](#)
- [1.5 Endocrine disorders](#)
- [1.6 Investigation of hormonal problems](#)

### **2. Growth**

- [2.1 Physiology of normal growth](#)
- [2.2 Assessment and investigation of growth disorders](#)
- [2.3 Short stature](#)
- [2.4 Tall stature](#)

### **3. Hypothalamus and pituitary glands**

- [3.1 Anatomy](#)
- [3.2 Physiology of the hypothalamus](#)
- [3.3 Hormone physiology of the anterior pituitary](#)
- [3.4 The neurohypophysis – posterior pituitary](#)
- [3.5 Pituitary disorders](#)
- [3.6 Investigation of hypothalamic and pituitary hormone disorders](#)
- [3.7 Principles of management of hypothalamic–pituitary disorders](#)

### **4. Puberty**

- [4.1 Physiology of normal puberty](#)
- [4.2 Clinical features of normal puberty](#)
- [4.3 Abnormal puberty](#)

## **5. Adrenal gland**

[5.1 Anatomy](#)

[5.2 Physiology](#)

[5.3 Disorders of the adrenal gland](#)

## **6. Thyroid gland**

[6.1 Anatomy](#)

[6.2 Physiology](#)

[6.3 Regulation](#)

[6.4 Functions of thyroid hormone](#)

[6.5 Investigation of thyroid disorders](#)

[6.6 Disorders of thyroid function](#)

## **7. Diabetes and hypoglycaemia**

[7.1 Physiology of glucose homeostasis](#)

[7.2 Diabetes mellitus](#)

[7.3 Hypoglycaemia](#)

## **8. Bone metabolism**

[8.1 Physiology of calcium and phosphate homeostasis](#)

[8.2 Disorders of calcium and phosphate metabolism](#)

[8.3 Investigation of bone abnormalities](#)

## **9. Miscellaneous endocrine disorders**

[9.1 Obesity](#)

[9.2 Multiple endocrine neoplasia syndromes](#)

[9.3 Autoimmune polyglandular syndromes](#)

[9.4 Endocrine complications of other disorders](#)

[9.5 Disorders of sexual development](#)

[9.6 Amenorrhoea](#)

## **10. Further reading**

---

# Endocrinology and Diabetes

---

## 1. HORMONES

### 1.1 Introduction

The endocrine system consists of a series of ductless glands that secrete the hormones that they produce into the bloodstream. The human fetus is dependent on endocrine development for hormones, which support normal development. Peripheral endocrine glands (thyroid, pancreas, adrenals and gonads) form early in the second month from epithelial/mesenchyme interactions. The fetus also has a unique hormonal system that combines not only its own developing endocrine system, but also that of the placenta and maternal hormones. In addition to the main endocrine glands, other important sources of hormones are the gastrointestinal tract, kidney, heart and adipose tissue.

### 1.2 Hormone physiology

#### Hormones

Hormones are chemical messengers produced by a variety of specialized secretory cells. They have effects on a wide range of biological processes. Hormones are classified according to their chemical nature:

- Amine: catecholamines, serotonin (5-hydroxytryptamine, 5HT)
- Peptide: growth hormone (GH), insulin, thyroxine
- Steroid: cortisol, aldosterone, androgens, oestrogen, progesterone

#### Mode of transmission

Hormone effects may be:

- Paracrine: a direct effect on nearby cells
- Autocrine: act on the tissue that secretes them
- Endocrine: carried by the circulation to a distant site of action

# Transport and metabolism

Most endocrine hormones are secreted into the systemic circulation, but those secreted from the hypothalamus are released into the pituitary portal system.

Many hormones are bound to proteins when in the circulation but only free hormones can exert their biological action on tissues. These binding proteins buffer against very rapid changes and act as a reservoir for the hormones.

Hormone	Hormone-binding proteins
Thyroxin	Thyroid-binding globulin, albumin
Testosterone/oestrogen	Sex hormone-binding globulin
Insulin-like growth factor-1	Insulin-like growth factor-binding proteins
Cortisol	Cortisol-binding protein

## Regulation

The effect and measured amount of a particular hormone in the circulation at any one time is the result of a complex series of interactions.

## Control and feedback

The rate of biosynthesis and secretion is controlled by negative feedback systems involving:

- Stimulating or releasing hormones
- Environmental effects
- Plasma concentrations of binding hormones
- Nutrient levels

Most hormones are controlled by some form of feedback. Insulin and glucose work on a feedback loop. Elevated glucose concentrations lead to insulin release, whereas insulin secretion is switched off when the glucose level decreases.

Receptor up- or downregulation also occurs. Downregulation leads to reduced sensitivity to a hormone and a reduced number of receptors after prolonged exposure to high hormone concentrations. A good example of this is the administration of intermittent gonadotrophin-releasing hormone (GnRH), which induces priming and facilitates a large output of gonadotrophins, whereas continuous GnRH leads to a downregulation of receptors and hence has a protective effect. However, this is not true of all pituitary hormones (e.g. ectopic adrenocorticotrophic hormone or ACTH secretion leads to receptor upregulation, which is the reverse process).

Hormones are usually metabolized in the liver or kidney but some are degraded peripherally (e.g. thyroid hormone) or in the plasma (e.g. catecholamines).

## Patterns of secretion

Individual hormones have different patterns of secretion which include:

- Continuous, e.g. thyroxine
- Pulsatile, e.g. follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH)
- Circadian, e.g. cortisol
- Stress related, e.g. ACTH
- Sleep related, e.g. GH, prolactin

## 1.3 Hormone–receptor interactions

Amine and peptide hormones have short half-lives (minutes) and act on cell-surface receptors. They often act via an intracellular second messenger (e.g. adenosine cyclic monophosphate or cAMP, calcium). Steroid hormones have longer half-lives (hours) and act on intracellular receptors. They act on DNA to alter gene transcription and protein synthesis. Thyroxine is the exception to this rule because it acts as a steroid hormone and binds to intracellular receptors.

## Hormone receptors

Hormones act by combining with a specific receptor protein which then starts the intracellular signal transduction pathway. There are two main types of receptor

1. Cell surface membrane receptors:
  - G-protein-coupled receptors (GPCRs)
  - Tyrosine kinase receptors (TKRs)
2. Intracellular receptors (for fat-soluble hormones)

### G-protein receptors

G-protein receptors are a large family of receptors that are integral to the cell-surface membrane and have seven transmembrane domains. The G-proteins may be inhibitory –  $G_i$  (e.g. somatostatin) – or stimulatory –  $G_s$  (e.g. all other hormones). When activated they cause dissociation of an intracellular trimeric G-protein which then acts via a second messenger. The intracellular messenger can be:

- **Adenosine cyclic monophosphate:** used by glucagon, ACTH, LH, FSH, PTH, calcitonin, adrenaline and noradrenaline
- **Guanine cyclic monophosphate (cGMP):** used by peptide hormones such as nitric oxide and atrial natriuretic hormone. The action of cGMP is opposed by phosphodiesterases
- **Inositol triphosphate system:** used by adrenaline and acetylcholine. The cytoplasmic enzyme phospholipase C (PLC) is activated and then releases inositol triphosphate from membrane phospholipids. These in turn release calcium from stores in the endoplasmic reticulum

### Tyrosine kinase receptors

The binding of the hormone results in dimerization and hence activation of the receptor. This may be



by phosphorylation of the receptor itself or by activation of cytoplasmic tyrosine kinase. Hormones activating this type of receptor include GH and insulin.

### **Intracellular receptors**

Receptors for the lipophilic hormones, e.g. steroids and thyroxine, are located within the cell cytoplasm or the nucleus. In nuclear receptors, the hormone receptor complex acts as a transcription factor binding to the promoter region of genes, hence modulating its expression. The nuclear receptor has a characteristic three-domain structure and is divided into three classes.

#### *Class I: steroid receptor family*

These receptors can be found in the cytoplasm bound to heat shock proteins (HSPs). The binding of the hormone leads to release of the HSP and the formation of a homodimer. This binds to hormone response elements at promoter sites.

#### *Class II: thyroid/retinoid family*

These are typically located in the nucleus. They function as heterodimers and are bound to response elements. Ligand binding leads to displacement of a co-repressor removing the suppression of gene activation.

#### *Class III: orphan receptor family*

No ligands have yet been identified.

## **1.4 Second messengers**

Some hormonal actions are carried out via second messengers.

Insulin-like growth factor-1 (IGF-1) and IGF-2 are GH-dependent peptide factors. They are believed to modulate many of the anabolic and mitogenic actions of GH. IGF-1 is important as a postnatal growth factor, whereas IGF-2 is thought to be essential for fetal growth.

## **1.5 Endocrine disorders due to receptor abnormalities**

- Syndromes of G-protein abnormalities, e.g. McCune–Albright syndrome
- Syndromes of receptor resistance: these mutations in nuclear receptors result in end-organ unresponsiveness, e.g. vitamin D-resistant rickets. The hormone levels are raised but the clinical picture is one of hormone insufficiency
- Mutations of nuclear receptors, e.g. pseudohypoparathyroidism

## **1.6 Investigation of hormonal problems**

In view of the complexities of control on the concentration of a particular hormone and the various factors that influence its distribution and elimination, the use of a single random measurement of a

hormone can be difficult to interpret. The plasma levels vary throughout the day because of pulsatile secretion, environmental stress or circadian rhythms. They are also influenced by the values of the substrates that they control. It is therefore often hard to define a normal range and dynamic testing may be required.

## **Blood hormone concentration measurements**

- Basal levels: those hormones in a steady state, e.g. thyroid function
- Timed levels: those hormones with levels that need to be interpreted with a normal range for the time of day, e.g. cortisol measured at 00:00 h and 08:00 h
- Stimulated: in suspected hormone deficiency, e.g. GH-stimulation tests
- Suppression: in conditions of hormone excess because hormone-producing tumours usually fail to show normal negative feedback, e.g. dexamethasone suppression test for suspected Cushing disease

## **Urine concentrations**

- Useful for identifying abnormalities in ratios of metabolites, e.g. diagnosis of the specific enzyme defect in congenital adrenal hyperplasia

# **2. GROWTH**

## **2.1 Physiology of normal growth**

### **Prenatal**

<b>Factors influencing intrauterine growth</b>
<ul style="list-style-type: none"><li>• Nutrition</li><li>• Genetic</li><li>• Maternal factors (smoking, blood pressure)</li><li>• Placental function</li><li>• Intrauterine infections</li><li>• Endocrine factors, e.g. IGF-2</li></ul>

### **Postnatal**

<b>Phases of postnatal growth</b>
<ul style="list-style-type: none"><li>• Nutrition</li><li>• Infancy: nutrition</li><li>• Childhood: GH (thyroxine)</li></ul>

- Puberty: sex hormones (GH)

Average growth during the pubertal phase is 30 cm (12 inches).

The genetics of growth is poorly understood but shows many characteristics of a polygenic model involving many genes. There are, however, some single gene growth defects including defects of human GH and the human GH receptor.

## 2.2 Assessment and investigation of growth disorders

The following parameters are important in the assessment of growth:

- Standing height
- Sitting height
- Head circumference
- Weight
- Skin-fold thicknesses
- Mid-arm circumference
- Pubertal status

### Auxology

When measuring height, the optimal method is for the child to be measured by the same trained measurer, on the same equipment and at the same time of day on each occasion in order to minimize measurement error. A stadiometer should be used and supine height measured at <2 years of age and standing height at >2 years.

A child's height may be compared with the population using centile charts, and also considered in terms of his or her genetic potential by comparison with the mid-parental height.

#### Mid-parental height

- Add 13 cm to mother's height to plot on a boy's chart
- Subtract 13 cm if plotting a father's height on a girl's chart
- Mid-parental height is half-way between the plotted corrected parental heights

The measurement of skin-fold thicknesses (e.g. triceps, subscapular) gives important information about body fat distribution, which changes at different ages. For example, in puberty there is an increase in truncal fat but a reduction in limb fat. Mean arm circumference can be used to assess muscle bulk.

To estimate the rate at which a child is growing it is necessary to measure the height on two separate occasions (at least 4–6 months apart) and divide the change in height by the period of time elapsed.

This is the height velocity and is expressed in centimetre per year. The height velocity can be plotted on standard reference charts.

## 2.3 Short stature

### Causes of short stature

- Familial
- Constitutional short stature, constitutional delay of growth and puberty
- Chronic illness:
  - Congenital heart disease
  - Respiratory disorders, e.g. cystic fibrosis
  - Renal failure
  - Gastrointestinal (GI) disorders: malabsorption, e.g. coeliac disease, Crohn disease
  - Neurological, e.g. intracranial tumours
- Endocrine:
  - GH insufficiency
  - Hypothyroidism
  - Cushing syndrome
- Dysmorphic syndromes:
  - Turner syndrome
  - Down syndrome
  - Low birthweight, e.g. Russell–Silver syndrome
  - Prader–Willi syndrome
- Skeletal dysplasia:
  - Achondroplasia
  - Hypochondroplasia
  - Mucopolysaccharidoses
  - Spondyloepiphyseal dysplasia
- Psychosocial/emotional deprivation

As a general rule, if a child has a normal growth rate then the cause of the short stature is in the past history, whereas a child with a low growth rate requires thought as to what current process(es) is causing the growth failure.

### Familial short stature

This remains one of the most common causes of short stature, whereby the child takes after the parents' heights and grows along a centile that is appropriate for their genetic potential.

### Constitutional short stature

This is a condition commonly seen in teenage boys who have a combination of delay in growth and

delay in puberty. There is often a history of a similar pattern of growth in male members of the family. Bone-age assessment (see below) is often the only investigation initially required and usually shows a delay. Children do reach their genetic potential, but later than their peers. Management consists primarily of reassurance and, in certain circumstances, the use of a short (<6-month) course of androgens to ‘kick start’ puberty.

Note that constitutional delay of growth and puberty should not be diagnosed in girls without thorough investigation.

## **Common syndromes associated with short stature**

### **Achondroplasia**

- Genetics:
  - Caused by mutations in the *FGFR3*, gene which provides the instructions for making a protein involved in the maintenance and development of brain and bone tissue. The inheritance is autosomal dominant but there are new mutations in 80%
- Clinical features:
  - Megalocephaly
  - Short limbs
  - Prominent forehead
  - Thoracolumbar kyphosis
  - Midfacial hypoplasia
  - Disproportionate short stature
- Radiology:
  - Diminishing interpeduncular distances between L1 and L5
- Complications:
  - Short stature
  - Dental malocclusion
  - Hydrocephalus
  - Repeated otitis media

### **Hypochondroplasia**

- Definition:
  - Rhizomelic short stature distinct from achondroplasia
- Inheritance:
  - About 70% affected individuals have mutations in the *FGFR3* gene
- Clinical features:
  - Affected individuals appear stocky or muscular
  - Usually recognized from age 2–3 years
  - Wide variability in severity
- Radiology:
  - No change in interpeduncular distances between L1 and L5
- Complications:

- Short stature

## **Mucopolysaccharidoses**

- Inheritance:
  - This can be autosomal recessive or X-linked recessive. Mucopolysaccharidoses (MPS) result from enzyme deficiencies that break down the complex carbohydrates called glycosaminoglycans
- Clinical features – depend on type of MPS:
  - Short spine and limbs
  - Coarse facial features
  - Reduced intelligence and abnormal behaviour in some forms
  - Hurler syndrome – shortened lifespan
  - Marked skeletal abnormalities and severe short stature in Morquio syndrome

## **Russell–Silver syndrome**

- Inheritance:
  - Sporadic: the genetic causes are complex but research has focused on genes located in particular regions of chromosomes 7 and 11. Parent-specific gene expression is also thought to play a role
- Definition:
  - Syndrome of short stature of prenatal onset
  - Occurrence is sporadic and aetiology is unknown
- Clinical features:
  - Short stature of prenatal onset
  - Limb asymmetry
  - Short incurved fifth finger
  - Small triangular face
  - Café-au-lait spots
  - Normal intelligence
  - Bluish sclerae in early infancy

## **Turner syndrome**

- Definition: a syndrome with a 45XO (or XO/XX or rarely XO/XY) karyotype associated with short stature, ovarian dysgenesis and dysmorphic features
- Inheritance: sporadic
- Clinical features:
  - Neonatal lymphoedema of hands and feet
  - Skeletal: short stature (mean adult height is 142 cm); widely spaced nipples, shield-shaped chest; wide carrying angle; short fourth metacarpal; hyperconvex nails
  - Facial: prominent, backward-rotated ears; squint, ptosis; high arched palate; low posterior hairline, webbed neck
  - Neurological: specific space–form perception defect
  - Endocrine: autoimmune diseases (hypothyroidism); type 2 diabetes; infertility and pubertal failure
  - Associations: horse-shoe kidneys; coarctation of the aorta; excessive pigmented naevi

Turner syndrome needs to be excluded in all girls whose height is below that expected for the mid-parental centile because not all girls with Turner syndrome show the classic phenotype.

## Assessment of a child with short stature

Measure and plot the child's and parents' height and see if child is growing along the predicted centile for genetic potential. Assess pubertal status according to Tanner stages (see [Section 4.2](#)). In teenage boys who are not yet in puberty, constitutional delay is the most likely.

History and clinical examination should identify an obvious chronic illness, which should then be specifically investigated. Features of recognized dysmorphic syndromes should be looked for. A child who is disproportionate should undergo skeletal survey to rule out a skeletal dysplasia.

## Investigation of short stature

- Full blood count
- Urea and electrolytes, C-reactive protein (CRP)
- Coeliac antibodies screen
- Thyroid function tests
- Karyotyping in females
- IGF-1 and IGF-BP3 levels
- Bone age
- GH provocation tests

### Bone age

This is a measure of the maturation of the epiphyseal ossification centres in the skeleton. Bone age proceeds in an orderly fashion and therefore defines how much growth has taken place and the amount of growth left. A delayed bone age may be caused by constitutional delay of growth and puberty, GH deficiency or hypothyroidism. An advanced bone age is caused by precocious puberty, androgen excess (e.g. congenital adrenal hyperplasia, CAH) and GH excess.

## 2.4 Tall stature

### Causes of tall stature in childhood

- Familial tall stature
- Constitutional obesity
- Precocious puberty
- Androgen excess:
  - Congenital adrenal hyperplasia
- GH excess
- Thyrotoxicosis

- Syndromes:
  - Cerebral gigantism (Sotos syndrome)
  - Marfan syndrome
  - Klinefelter syndrome
  - Familial tall stature

This is a child of tall parents whose height follows a centile line above, yet parallel to, the 97th centile, which is appropriate for the predicted mid-parental centile.

## Constitutional obesity

Remember: if a child is tall and fat it is most probably due to constitutional obesity. These children often have a slightly advanced bone age and go into puberty relatively early (not precocious) and thus end up appropriate (or slightly tall) for parents' heights.

## Syndromes of tall stature

### Marfan syndrome

- Inheritance:
  - Autosomal dominant. Caused by mutations in the *FBNI* gene which codes for fibrillin – 1. 25% of affected individuals have a new mutation
- Clinical features:
  - Skeletal:
    - Arachnodactyly
    - Tall stature
    - Scoliosis
    - High arched palate
    - Pectus excavatum/carinatum
    - Joint hypermobility
  - Central nervous system (CNS):
    - Learning disabilities
  - Ocular:
    - Lens dislocation
  - Cardiovascular system:
    - Aortic dissection
    - Mitral valve prolapse
  - Respiratory:
    - Pneumothorax

### Klinefelter syndrome

- Definition:
  - Karyotype 47XXY



- Inheritance:
  - Sporadic
- Clinical features:
  - Tall and slim
  - Cryptorchidism
  - Gynaecomastia
  - Learning disability
  - Azoospermia and infertility
  - Immature behaviour

### **Sotos syndrome (cerebral gigantism)**

- Inheritance:
  - Sporadic caused by mutations in the *NSDI* gene
- Clinical features:
  - Birthweight and length >90th centile
  - Excessive linear growth during the first few years (which characteristically falls back)
  - Head circumference is proportional to length
  - Large hands and feet
  - Large ears and nose
  - Intellectual retardation
  - Clumsiness

### **Assessment of a child with tall stature**

Measure child and parents' heights and compare with weight. Assess pubertal status. History and clinical examination should identify an obvious cause or syndrome that can then be investigated.

### **Investigation of tall stature**

- Thyroid function
- Bone age
- Skeletal survey
- Karyotype

## **3. HYPOTHALAMUS AND PITUITARY GLANDS**

The hypothalamic–pituitary axis is of vital importance because it regulates many of the other endocrine glands in the body.

### **3.1 Anatomy**

# Hypothalamus

The hypothalamus lies between the preoptic area and the mamillary bodies. It interacts with the frontal cortex, thalamus limbic system and brain stem. The axonal processes extend down into the median eminence where regulatory hormones are secreted into the portal circulation.

## Pituitary gland

The pituitary gland is a midline structure situated inferior to the hypothalamus within the pituitary fossa. It consists of three lobes: the anterior and posterior lobes with a small intervening intermediate lobe. The anterior and intermediate lobes are derived from the buccal mucosa whereas the posterior lobe is derived from neural ectoderm. The anterior pituitary has five neuroendocrine cell types each defined by the hormone they produce: corticotrophs (ACTH), somatotrophs (GH), gonadotrophs (LH, FSH), thyrotrophs (thyroid-stimulating hormone or TSH) and lactotrophs (prolactin or PRL). The posterior pituitary secretes oxytocin and antidiuretic hormone.

The development of the normal pituitary gland relies on a number of transcription factors called homeobox genes and *Prop-1* (prophet of *Pit-1*) is a homeobox gene necessary for the development of GH-, PRL- and thyrotrophin-producing cells. *HESX1* is a homeobox gene implicated in some forms of septo-optic dysplasia.

## 3.2 Physiology of the hypothalamus

The hypothalamus plays important roles in appetite suppression and temperature control. Leptin is a hormone encoded by the *ob* gene which is expressed primarily by adipocytes. Leptin provides the body with information about nutritional status. The hypothalamus contains large numbers of leptin receptors and plays an important role in controlling feeding behaviour and hunger. Leptin also plays a significant role in the regulation of reproduction. Ghrelin is a gastric peptide that stimulates GH secretion and increases adiposity. It acts at the GH secretagogue receptors located in the hypothalamus and pituitary gland. Data also suggest a role for neuropeptide Y in the regulation of body fat and its regulation by leptin.

## 3.3 Hormone physiology of the anterior pituitary

### Growth hormone

#### Structure

GH is a 191-amino acid peptide (22 kDa) secreted by somatotrophs. It circulates in the unbound form and also bound to binding proteins, which are portions of the extracellular receptor domain.

#### Function

GH has direct effects on carbohydrate and lipid metabolism. The growth-promoting effects of GH are

mediated by somatomedin C (otherwise known as IGF-1), which is produced in the liver cells after GH binding to cell-surface receptors and results in gene transcription. IGF-1 and IGF-2 are 70-amino acid peptides, structurally related to insulin. IGF-1 increases the synthesis of protein, RNA and DNA, increases the incorporation of protein into muscle and promotes lipogenesis. The IGFs are bound to a family of binding proteins (IGFBP-1 to -6), of which IGFBP-3 predominates. These binding proteins not only act as transporters for the IGFs, but also increase their half-life and modulate their actions on peripheral tissues.

## **Regulation**

GH secretion is pulsatile, consisting of peaks and troughs. Nocturnal release occurs during non-dreaming or slow-wave sleep, shortly after the onset of deep sleep. There is a gradual increase in GH production during childhood, a further increase (with increased amplitude of peaks) during puberty secondary to the effect of sex steroid, followed by a postpubertal fall.

Three peptides are critical to the control of GH secretion:

- Growth hormone-releasing hormone (GHRH)
- Growth hormone-releasing peptide (GHRP) – ghrelin
- Somatostatin

These peptides mediate stimulation, inhibition and feedback suppression of GH secretion, and form the final common pathway for a network of factors that influence the secretion of GH, which include sex steroids, environmental inputs and genetic determinants.

GHRH and somatostatin act via the activation of G-protein receptors on the somatotrophs, increasing or reducing cAMP and intracellular  $\text{Ca}^{2+}$ . GHRH stimulates GH release, whereas somatostatin inhibits both GH synthesis and its release. GH and IGF-1 exert a tight feedback control on somatostatin, and probably also on GHRH. GHRP – ghrelin – is an oligopeptide derivative of enkephalin and is a 28-peptide residue predominantly produced by the stomach. It requires fatty acylation of the N-terminal serine for biological activity. Ghrelin is released in response to acute and chronic changes in nutritional state. The concentrations of ghrelin fall postprandially and in obesity, and rise during fasting, after weight loss or gastrectomy, and in anorexia nervosa. GHRP and GHRH act synergistically in the presence of a functioning hypothalamic–pituitary axis.

## **Gonadotrophins**

### **LH and FSH**

#### **Structure**

LH and FSH are glycoproteins composed of an  $\alpha$  and a  $\beta$  subunit. The  $\alpha$  subunits are identical to other glycoproteins within the same species, whereas the  $\beta$  subunits confer specificity.

#### **Function**

In the male, Leydig cells respond to LH, which stimulates the first step in testosterone production. In the female, LH binds to ovarian cells and stimulates steroidogenesis.

FSH binds to Sertoli cells in the male, increases the mass of the seminiferous tubules and supports the development of sperm. In the female, FSH binds to the glomerulosa cells and stimulates the conversion of testosterone to oestrogen.

### **Regulation**

Gonadotrophin-releasing hormone (GnRH) is released in a pulsatile fashion, which stimulates the synthesis and secretion of LH and FSH. Expression and excretion of FSH are inhibited by inhibin, a gonadal glycoprotein. This has no effect on LH. In the neonate there are high levels of gonadotrophins and gonadal steroids. These decline progressively until a nocturnal increase occurs, leading up to the onset of puberty (amplification of low-amplitude pulses).

## **Thyroid-stimulating hormone**

### **Structure**

TSH is a glycoprotein containing the same  $\alpha$  subunit as LH and FSH but a specific  $\beta$  subunit.

### **Function**

TSH is a trophic hormone and hence its removal reduces thyroid function to basal levels. It binds to surface receptors on the thyroid follicular cell and works via activation of adenylyl cyclase to cause the production and release of thyroid hormone.

### **Regulation**

TSH synthesis and release are modulated by thyrotrophin-releasing hormone (TRH), which is produced in the hypothalamus and secreted into the hypophyseal portal veins, from where it is transported to the anterior pituitary gland. TRH secretion is influenced by environmental temperature, somatostatin and dopamine. Glucocorticoids inhibit TSH release at a hypothalamic level.

## **Adrenocorticotrophic hormone**

### **Structure**

ACTH is a 39-amino acid peptide cleaved from a large glycosylated precursor (pro-opiomelanocortin or POMC) which also gives rise to melanocyte-stimulating hormone (MSH) and  $\beta$ -endorphin.

### **Function**

ACTH is responsible for stimulation of the adrenal cortex, in particular the production of cortisol. Hypothalamic control of its function is evident in the late-gestation fetus. ACTH plays a role in fetal adrenal growth.

### **Regulation**

Corticotrophin-releasing hormone (CRH) stimulates ACTH release via increasing cAMP levels. Arginine vasopressin (AVP) also stimulates ACTH release and potentiates the response to CRH.

# **Prolactin**

## **Structure**

Prolactin has a similar amino acid sequence to GH, and acts via the lactogenic receptor, which is from the same superfamily of transmembrane receptors as the GH receptor.

## **Function**

Prolactin is responsible for the induction of lactation and cessation of menses during the puerperium. During the neonatal period, prolactin levels are high secondary to fetoplacental oestrogen. It then falls and remains consistent during childhood but there is a slight rise at puberty.

## **Regulation**

Dopamine inhibition from the hypothalamus.

## **3.4 The neurohypophysis – posterior pituitary**

### **Water regulation**

The body maintains water balance by regulating fluid intake and output. There is a narrow range of normal serum osmolality between 280 and 295 mosmol/l.

#### **Output**

Controlled by:

- Hypothalamic osmoreceptors and neighbouring neurons that secrete AVP
- Concentrating effect of the kidney

#### **Input**

Controlled by:

- Hypothalamic thirst centre

### **Arginine vasopressin**

#### **Structure**

AVP is a nonapeptide containing a hexapeptide ring. It is produced as a pro-hormone in the supra-optic and paraventricular nuclei. Action potentials from the hypothalamus cause its release from the posterior pituitary gland into the circulation.

#### **Regulation**

This is largely by the osmolality of extracellular fluid and haemodynamic factors. The release of AVP is modulated by stimulatory and inhibitory neural input. Noradrenaline inhibits AVP release and cholinergic neurons facilitate it.

## Physiology

The normal mature kidney is able to produce urine in a concentration range of 60–1100 mosmol/kg. The ability to vary urine concentration depends on the spatial arrangements and permeability characteristics of the segments of the renal tubules.

AVP regulates the permeability of the luminal membrane of the collecting ducts. Low permeability in the presence of a low AVP concentration leads to dilute urine.

## 3.5 Pituitary disorders

### Anterior pituitary

- Congenital:
  - Agenesis of the corpus callosum
  - Structural abnormalities:
    - Septo-optic dysplasia
    - Pituitary hypoplasia
  - Idiopathic hormonal abnormalities:
    - Isolated GH deficiency
    - Idiopathic precocious puberty
- Acquired:
  - Excess:
    - Intracranial tumours
    - Cushing disease – pituitary adenoma
  - Deficiency, e.g. secondary to treatment with radiation or surgery:
    - Pituitary damage
    - Tumours
    - Surgery
    - Radiotherapy
    - Trauma

### Septo-optic dysplasia (De Morsier syndrome)

A developmental anomaly of the midline structures of the brain. Classically characterized by:

- Absence of septum pellucidum and/or corpus callosum
- Optic nerve hypoplasia
- Pituitary hypoplasia with variable pituitary hormone deficiencies (most commonly this is GH deficiency which may either be isolated or progress to an evolving endocrinopathy)

Treatment is by hormone replacement and management of visual difficulties.

### Craniopharyngioma

This is one of the most common supratentorial tumours in children. It commonly presents with headaches and visual field defects. On imaging, the tumour is frequently large and cystic. Treatment is by resection plus radiotherapy if initial resection is incomplete or recurrence occurs.

Postoperative hormonal deficiencies are common, involving both anterior and posterior pituitary hormones. Treatment is by hormonal supplementation. There is also the risk of hypothalamic damage. Remember: the hypothalamus is responsible for other effects that are not so easily treated by replacement therapy, e.g. temperature, appetite and thirst control. The obesity associated with hypothalamic damage (secondary to hyperphagia) is very difficult to manage and has a poor prognosis. The maintenance of fluid homeostasis in children with the combination of diabetes insipidus and adipsia (loss of thirst sensation) can be a challenge.

### **Acquired endocrine problems secondary to tumours and/or their treatment**

- Short stature
- Pubertal delay or arrest
- Precocious puberty
- Thyroid tumours
- Infertility
- Hypopituitarism – isolated or multiple
- Gynaecomastia

### **Posterior pituitary**

#### **Diabetes insipidus**

Defined as insufficient AVP causing a syndrome of polyuria and polydipsia. With an intact thirst mechanism copious water drinking maintains normal osmolalities. However, problems with the thirst mechanism or insufficient water intake lead to hypernatraemic dehydration.

It is important to remember that cortisol is required for water excretion. Therefore in children with combined anterior and posterior pituitary dysfunction, there is a risk of dilutional hyponatraemia if they are cortisol deficient and receiving DDAVP (1-deamino-8-D-arginine vasopressin) treatment. Hence the emergency management of the unwell child is to increase the hydrocortisone treatment and to stop the DDAVP.

### **Causes of diabetes insipidus**

- Central:
  - Craniopharyngioma
  - Germinoma
  - Langerhans cell histiocytosis (LCH)
  - Idiopathic
  - Trauma
- Nephrogenic:
  - X-linked nephrogenic diabetes insipidus

- Secondary to renal damage

## **Syndrome of inappropriate ADH (SIADH) secretion**

Defined by the criteria of:

- Water retention with hypo-osmolality
- Normal or slightly raised blood volumes
- Less than maximally dilute urine
- Urinary sodium > sodium intake

## **Causes of SIADH**

- CNS disorders: meningitis, abscess; trauma; hypoxic–ischaemic insult
- Respiratory tract disease: pneumonia; cavitation
- Reduced left atrial filling: drugs
- Malignancies: lymphoma; bronchogenic carcinoma; idiopathic

### *Management of SIADH*

Management focuses on treatment of the underlying cause and management of the fluid and electrolyte imbalance. Accurate input and output charts are required as are twice daily weights in the initial period of assessment. Fluid restriction is the mainstay of management.

## **3.6 Investigation of hypothalamic and pituitary hormone disorders**

### **Anterior pituitary stimulation tests**

Many hormones (e.g. GH, LH and FSH) are secreted in a pulsatile fashion, and therefore a random measurement of the concentration of the circulating hormone is often inadequate for diagnosing a deficiency disorder.

Hormone measurement tests include:

- GH release/ACTH (via cortisol response): insulin tolerance test/glucagon stimulation test
- TSH/prolactin response: TRH test
- FSH/LH response: LHRH test

### **GH tests**

Provocation tests of GH are potentially hazardous. Insulin tolerance tests should be performed only in specialist centres because of the risk of severe hypoglycaemia. Other GH provocation tests include the use of glucagon, arginine and clonidine. Physiological tests of GH secretion include a 24-h GH profile and measurement of GH after exercise or during sleep.



## **Combined pituitary function test**

The standard test involves the intravenous injection of either insulin or glucagon in combination with TRH and LHRH (in the pubertal child).

Blood samples are taken at 0 min (before stimulation), 20, 30, 60, 90 and 120 min.

After insulin administration, a profound hypoglycaemia results in 20 min which needs to be corrected by the use of an oral glucose solution or the judicious use of intravenous 10% dextrose. (Remember: the rapid correction of hypoglycaemia with a hypertonic glucose solution can result in cerebral oedema.)

GH concentrations rise at 30 min after insulin, or 60–90 min after glucagon injection. A rise to over 6 mg/l rules out GH deficiency.

A normal TSH response to TRH is a rise at 20 min post-dose and then a fall by 60 min. A continued rise of TSH at 60 min implies hypothalamic damage. Secondary hypothyroidism is demonstrated by a low baseline TSH level, whereas primary hypothyroidism is associated with a raised TSH.

A raised baseline prolactin level suggests a lack of hypothalamic inhibition of its release. Under normal circumstances, after the administration of TRH, prolactin would be expected to rise at 20 min and then to be falling by 60 min.

In the absence of precocious puberty, the LHRH test will demonstrate only a rise in FSH and LH at 20 and 60 min during the first 6 months of life and in the peripubertal period. Raised baseline gonadotrophin levels reflect gonadal failure.

## **Posterior pituitary function tests**

- Paired urine and serum osmolalities
- Water deprivation test

The child is weighed in the morning and is then deprived of water for a maximum of 7 h, during which time the child's weight, pulse rate and blood pressure, and urine osmolality are measured hourly.

Plasma sodium levels and osmolality are measured every 2 h.

The test is terminated if the patient's weight falls by 5% from the starting weight, serum osmolality rises ( $>295$  mosmol/kg of water) in the face of an inappropriately dilute urine ( $<300$  mosmol/kg) or if the patient becomes significantly clinically dehydrated/clinically unwell.

A diagnosis of diabetes insipidus (DI) may be made in the presence of a plasma osmolality  $>290$  mosmol/kg of water with an inappropriately low urine osmolality.

The child is then given a dose of DDAVP and the urine and plasma osmolality are then measured. A rise in urine concentration confirms a diagnosis of central DI, whereas a child with nephrogenic DI will fail to concentrate urine after DDAVP.

### 3.7 Principles of management of hypothalamic–pituitary disorders

#### Treatment of anterior pituitary deficiencies

When specific hormones or their stimulating hormones are deficient the actual hormone may be replaced, e.g.:

- Lack of GH response: replace with GH

However, if the deficient hormone is a trophic or regulatory hormone then it is the target hormone that is replaced, e.g.:

- Lack of TFT: replace with thyroxine
- Low gonadotrophins: replace with testosterone in males, oestrogen in females
- ACTH: replace with hydrocortisone
- Vasopressin: replace with DDAVP

#### Growth hormone treatment

The following are the licensed indications for treatment with GH.

These recommendations have been endorsed by the National Institute for Health and Clinical Excellence (NICE):

- Documented GH deficiency – congenital or acquired
- Turner syndrome
- Chronic renal failure
- Prader–Willi syndrome
- Small for gestational age

GH deficiency should be treated by a specialist who has experience of managing children with growth disorders. Most regimens involve daily injections with different doses of GH depending on the indications. Close local community liaison is required for this.

#### Panhypopituitarism

Panhypopituitarism is much less common than isolated hormone deficiency and may develop as an evolving endocrinopathy. Management includes replacement with GH, thyroxine, cortisol during childhood with induction and maintenance of puberty with the appropriate sex hormone (testosterone

or estradiol). Parents of children who are cortisol or ACTH deficient should be given written instructions and training in the management of an acute illness and must have emergency supplies of intramuscular hydrocortisone available at all times.

## Treatment of posterior pituitary deficiencies

### Central diabetes insipidus

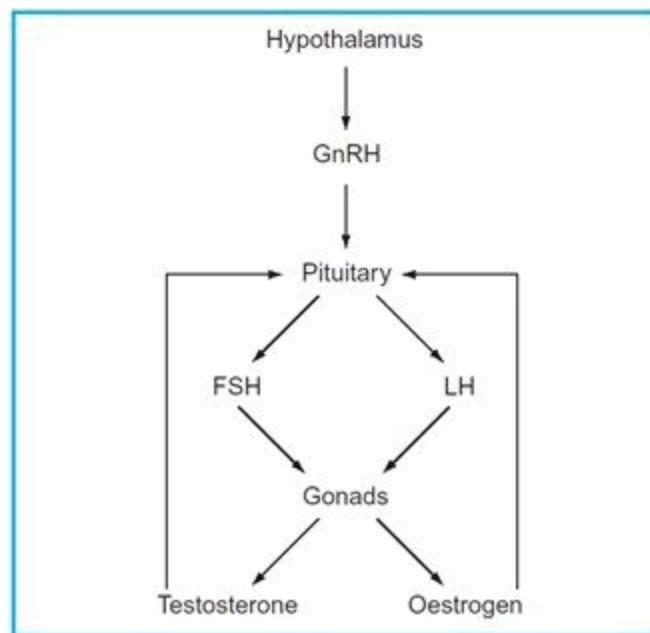
- Treatment with DDAVP (desmopressin) as either a nasal spray or tablets

## 4. PUBERTY

### 4.1 Physiology of normal puberty

The clinical manifestations of normal pubertal development occur secondary to sequential changes in endocrine activity.

### Hormonal control of puberty



Hormonal control of puberty.

The pulsatile release of GnRH from the hypothalamus leads to the secretion of LH and FSH from the gonadotrophin cells of the pituitary gland.

In the male, Leydig cells respond to LH, which stimulates the first step in testosterone production. In the female, LH binds to ovarian cells and stimulates steroidogenesis. FSH binds to Sertoli cells in the male where it increases the mass of the seminiferous tubules and supports the development of sperm. In the female, FSH binds to the granulosa cells and stimulates the conversion of testosterone to

oestrogen.

## **Sex steroids**

Testosterone is produced by the Leydig cells of the testes. It is present in the circulation bound to sex hormone-binding globulin (SHBG). Free testosterone is the active moiety at the level of target cells. Testosterone is then converted either to dihydrotestosterone (DHT) by  $5\alpha$ -reductase or to oestrogen by aromatase. Both DHT and testosterone attach to nuclear receptors, which then bind to steroid-responsive regions of genomic DNA to influence transcription and translation.

Oestrogen is produced by the follicle cells of the ovary. The main active form of oestrogen is estradiol. This circulates bound to SHBG and causes growth of the breasts and uterus, and the female distribution of adipose tissue, and increases bone mineralization.

### **Inhibin**

Inhibin is a glycoprotein produced by Sertoli cells in males and granulosa cells in females.

### **SHBG**

Androgens reduce SHBG formation, and oestrogens stimulate its formation. Therefore increased free testosterone levels magnify androgen effects.

## **Hormonal regulation**

In the presence of GnRH the gonadotrophins are controlled by the sex steroids and inhibin. LH and FSH levels are under the influence of negative feedback mechanisms in both the hypothalamus and the pituitary. Inhibin inhibits only FSH and acts at the level of the pituitary.

Positive feedback also occurs during mid-puberty in females. Increased oestrogen primes gonadotrophins to produce LH until, at a critical stage at the middle of the menstrual cycle, a large surge occurs causing ovulation.

## **4.2 Clinical features of normal puberty**

The physical changes of pubertal development may be described by an objective method derived by Tanner.

### **Tanner stages**

#### **Male genitalia development**

Stage 1: pre-adolescent

Stage 2: enlargement of scrotum and testes and changes in scrotal skin

Stage 3: further growth of testes and scrotum; enlargement of penis

Stage 4: increase in breadth of penis and development of glans; further growth of scrotum and testes  
Stage 5: adult genitalia in shape and size

## **Female breast development**

Stage 1: pre-adolescent  
Stage 2: breast-bud formation  
Stage 3: further enlargement and elevation of breast and papilla with no separation of their contours  
Stage 4: projection of areola and papilla to form a secondary mound above the level of the breast  
Stage 5: mature stage with projection of papilla only

## **Pubic hair**

Stage 1: pre-adolescent  
Stage 2: sparse growth of long, slightly pigmented, downy hair  
Stage 3: hair spread over junction of the pubes, darker and coarser  
Stage 4: adult-type hair, but area covered is smaller  
Stage 5: adult in quantity and type

## **Axillary hair**

Stage 1: no axillary hair  
Stage 2: scanty growth  
Stage 3: adult in quantity and type

Puberty starts on average at age 12 years in boys and 10 years in girls. As nutrition and health improve, the age of onset of puberty is becoming earlier with each generation.

In the male, acceleration in growth of the testes (from a prepubertal 2 ml volume) and scrotum is the first sign of puberty. This is followed by reddening and rugosity of scrotal skin, and later by development of pubic hair, penile growth and axillary hair growth.

A 4 ml testicular volume signifies the start of pubertal change.

Peak height velocity occurs with testicular volumes of 10–12 ml.

In the female, the appearance of the breast bud and breast development are the first sign of puberty. It is due to production of oestrogen from the ovaries. This is followed by the development of pubic and axillary hair, which is controlled by the adrenal gland. Peak height velocity coincides with breast stage 2–3. Menarche occurs late at breast stage 4, by which stage growth is slowing down. Most girls have attained menarche by age 13 years.

## **Body composition**

Prepubertal boys and girls have equal lean body mass, skeletal mass and body fat. The earliest

change in puberty is an increase in lean body mass.

## **Growth spurt**

The pubertal growth spurt is the most rapid phase of growth after the neonatal period. This is an early event in girls and occurs approximately 2 years earlier than in boys, i.e. at a mean age of 12 years. The mean height difference between males and females of 12.5 cm is due to the taller male stature at the time of pubertal growth spurt and increased height gained during the pubertal growth spurt.

## **Adrenarche**

Adrenal androgens, dehydroepiandrosterone sulphate (DHEAS) and androstenedione, rise approximately 2 years before gonadotrophins and sex steroids rise. Adrenarche begins at 6–8 years of age and continues until late puberty. Control of this is unknown. Adrenarche does not influence onset of puberty.

## **Gynaecomastia**

Gynaecomastia is physiological and occurs in 75% of boys to some degree (usually during the first stages of puberty), but most regress within 2 years. Management is by reassurance, support and weight loss if obesity is a factor.

### **Causes of gynaecomastia**

- Normal puberty (common)
- Obesity (common)
- Klinefelter syndrome
- Partial androgen insensitivity

## **4.3 Abnormal puberty**

- Early (precocious):
  - <9 years in boys
  - <8 years in girls
- Discordant (abnormal pattern)
- Delayed:
  - >14 years in boys
  - >13 years in girls

## **Precocious puberty**

### **Definition**

Central precocious puberty is consonant with puberty (i.e. occurs in the usual physiological pattern of development but at an earlier age). It is due to premature activation of the GnRH pulse generator. In girls, often no underlying cause is found; however, it is almost always pathological in males.

### **Causes of true precocious puberty (gonadotrophin dependent)**

- Idiopathic
- CNS tumour
- Neurofibromatosis
- Septo-optic dysplasia – in this rare condition precocious puberty may occur in the presence of deficiencies of other pituitary hormones (see [Section 2.4](#))

### **Causes of gonadotrophin-independent precocious puberty**

- McCune–Albright syndrome (usually due to ovarian hypersecretion)
- Testicular/ovarian tumours
- Liver or adrenal tumours – may cause virilization

### **Useful tests for the investigation of precocious puberty**

- Estradiol/Testosterone
- Adrenal androgens, including 17-hydroxyprogesterone
- LHRH stimulation test
- Bone age
- Pelvic ultrasound scan
- Brain magnetic resonance imaging (MRI)
- Abdominal computed tomography (CT) if adrenal/liver tumour suspected

### **Management of precocious puberty**

A GnRH analogue (GnRHa) may be used to halt the progression of puberty. Children who enter puberty early are tall initially, but end up as short adults due to premature closure of epiphyses. Although GH has been used in addition to GnRHa, there is no clear evidence that final height is improved.

### **Discordant puberty (abnormal pattern)**

- Breast development only – gonadotrophin-independent precocious puberty, e.g. McCune–Albright syndrome
- Inadequate breast development, e.g. gonadal dysgenesis, Poland anomaly
- Androgen excess – pubic hair, acne, clitoral enlargement, e.g. CAH, Cushing disease, polycystic ovarian syndrome (PCO), adrenal neoplasm
- Inadequate pubic hair, e.g. androgen insensitivity, adrenal failure
- No menarche, e.g. polycystic ovaries/rarely absent, abnormal uterus, imperfect hymen
- No growth spurt, e.g. hypothalamic–pituitary disorders, skeletal dysplasias

## Premature thelarche

- Usually in girls aged between 1 and 3 years
- Isolated breast development (never more than stage 3)
- No other signs of puberty
- Normal growth velocity for age
- Normal bone age
- Prepubertal gonadotrophin levels
- Progress to puberty at normal age

## Delayed puberty

### *Definition*

No signs of puberty at an age when pubertal change would have been expected.

## Causes of delayed puberty

- Constitutional delay of growth and puberty
- Hypothalamic or pituitary disorders:
  - Hypogonadotrophic hypogonadism
  - Idiopathic
  - Pituitary tumours
  - Post-central irradiation
  - Post-intracranial surgery
  - Post-chemotherapy
  - Anorexia nervosa
- Systemic disease
- Kallman syndrome – hypogonadotrophic hypogonadism with anosmia
- Gonadal dysgenesis:
  - Turner syndrome
  - Hypothyroidism

At least 17 different single gene mutations are recognized to cause delayed puberty in humans. Several of these genes are involved in the development of the olfactory system and are frequently associated with the clinical features of Kallman syndrome. The *KAL1* gene codes for a protein called anosmin 1 which helps control the growth and migration of neurons that form the olfactory bulb and those that produce GnRH.

## Investigation of delayed puberty in boys

In otherwise well boys with short stature and delayed puberty the most likely cause is constitutional delay. Initially this requires no investigations apart from a bone age. If after a trial of treatment there is no progression of puberty, further investigations may be needed including the following:

- In boys:



- LH, FSH, testosterone
- LHRH test
- Karyotyping
- In girls, delayed puberty must always be investigated:
  - Karyotyping
  - LH, FSH, oestrogen
  - LHRH test
  - Pelvic ultrasonography

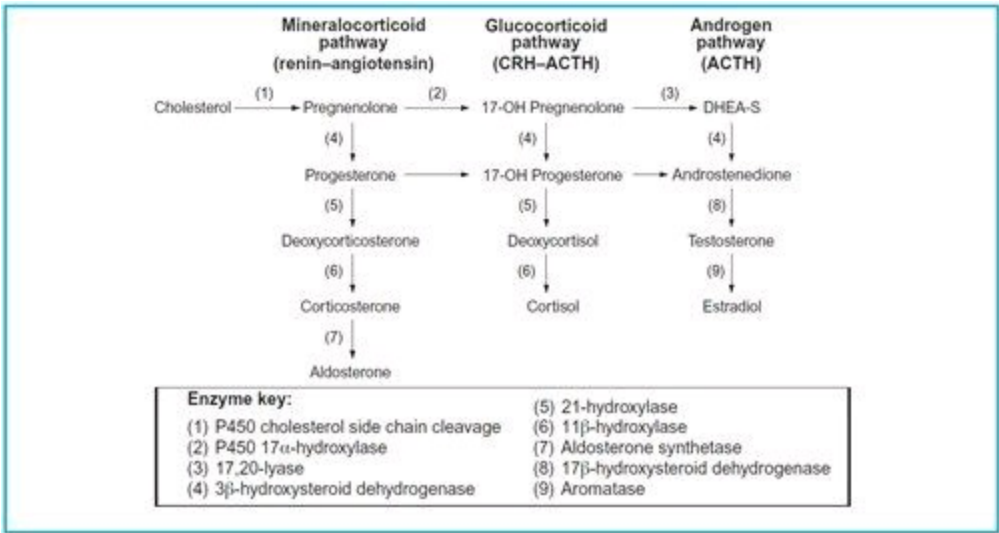
## Treatment

### *Constitutional delay*

- Reassurance
- Androgens: oxandrolone orally daily or depot testosterone injection monthly
- Reassess at 4–6 months

### *Other causes of delayed puberty*

- Treat underlying cause
- Induce and maintain puberty with testosterone in boys, ethinylestradiol in girls



Pathways of adrenal hormone synthesis.

## 5. THE ADRENAL GLAND

### 5.1 Anatomy

The adrenals are triangular in shape and located at the superior pole of the kidneys. Each adrenal gland is made up of cortex, arising from mesoderm at the cranial end of the mesonephros, and medulla, which arises from neural crest cells.

The cortex consists of three zones:

- Zona glomerulosa: produces aldosterone
- Zona fasciculata: produces cortisol/androstenedione
- Zona reticularis: produces DHEAS

## 5.2 Physiology

### Cortex

The adrenal cortex has three principal functions:

- Glucocorticoid production (cortisol)
- Mineralocorticoid production (aldosterone)
- Androgen production (testosterone, androstenedione)

### Glucocorticoids

Cortisol is the principal glucocorticoid. It plays a vital role in the body's stress response and is an insulin counter-regulatory hormone increasing gluconeogenesis, hepatic glycogenolysis, ketogenesis necessary for the action of other hormones, e.g. noradrenaline, adrenaline, glucagons.

It influences other organ physiology:

- Normal blood vessel function
- Cardiac and skeletal muscle
- Nervous system
- Inhibition of the inflammatory response of tissues to injury
- Secretion of a water load

Cortisol secretion is under pituitary control by ACTH. ACTH has a circadian rhythm, being at its lowest at midnight and rising in the early morning. There is also a negative feedback loop from cortisol. ACTH acts via cAMP and causes a flux of cholesterol through the steroidogenic pathway.

### Mineralocorticoids

Aldosterone has the main mineralocorticoid action:

- It increases sodium reabsorption from urine, sweat, saliva and gastric juices in exchange for potassium and hydrogen

The secretion of aldosterone is primarily regulated by the renin–angiotensin system, which is responsive to electrolyte balance and plasma volumes. Hyponatraemia and hyperkalaemia can also have a direct aldosterone stimulatory effect. ACTH can produce a temporary rise in aldosterone but

this is not sustained.

## Renin

Renin is a glycoprotein synthesized in the juxtaglomerular apparatus, and stored as an inactive pro-enzyme in cells of the macula densa of the distal convoluted tubule. Its release is stimulated by reduced renal perfusion, hyperkalaemia and hyponatraemia.

Renin hydrolyses angiotensin to form angiotensin I (an  $\alpha_2$ -globulin synthesized in the liver). This is converted to angiotensin II by angiotensin-converting enzyme (ACE). ACE is present in high concentrations in the lung, but is also widely distributed in the vasculature for local angiotensin II release.

## Adrenal androgens

These include testosterone, androstenedione and DHEAS. Secretion varies with age and, although responsive to ACTH, do not always parallel the cortisol response.

## 5.3 Disorders of the adrenal gland

### Medulla

#### Phaeochromocytoma

Catecholamine-secreting tumour. Malignancy is uncommon, but 10% are bilateral. Catecholamine excess leads to sustained hypertension. Phaeochromocytomas are associated with von Recklinghausen disease, von Hippel–Landau disease and syndromes of multiple endocrine neoplasia (MEN).

#### *Investigation*

- MIBG (*meta*-iodobenzylguanidine) isotope scans
- Plasma and urine catecholamine measurement

#### *Management*

The management of phaeochromocytoma is by surgical excision. Preoperative management requires both  $\alpha$ - and  $\beta$ -adrenoceptor blockade in order to prevent an acute hypertensive crisis or cardiac dysrhythmias.

### Cortex

#### Adrenal insufficiency

#### *Causes*

- Primary:
  - Idiopathic

- Congenital adrenal hyperplasia
- Adrenal haemorrhage
- Addison disease
- TB
- Autoimmune disease
  - Iatrogenic
- Secondary:
  - Pituitary hypoplasia
  - Isolated ACTH deficiency
  - Panhypopituitarism
  - Tumour, e.g. craniopharyngioma

## **Addison disease**

- Definition:
  - Adrenal hypofunction
- Aetiology:
  - Autoimmune
  - Secondary to TB
  - Associated with adrenal leukodystrophy
- Presentation:
  - Often with non-specific symptoms of tiredness and abdominal pain
  - May present with collapse related to a salt-losing crisis

### *Investigation of adrenal cortical insufficiency*

- The Synacthen test, which assesses the ability of the stimulated adrenal glands to mount a hormone response. A dose of synthetic ACTH is given and the cortisol level measured after 30 and 60 min. A normal adrenal response would be a cortisol level  $>450\text{--}550\text{ nmol/l}$  at 30 min
- A 24-h blood cortisol profile assesses the natural secretion from the adrenal gland. This would be expected to show the normal diurnal rhythm of cortisol secretion, with an increase in the morning and a nadir at midnight

### *Treatment*

Glucocorticoid and mineralocorticoid replacement using hydrocortisone and fludrocortisone, respectively. At the time of illness, injury or acute stress, the body naturally increases the output of corticosteroids from the adrenal glands. A person on replacement hydrocortisone needs to mimic this process and to increase his or her hydrocortisone at these times. It is therefore important that a steroid user's card is carried at all times to alert medical professionals at the time of an emergency.

## **Adrenal steroid excess (Cushing syndrome)**

Cushing syndrome is a syndrome of cortisol excess. Cushing disease is the term used when this is secondary to a pituitary ACTH-producing tumour (adenoma).

### *Causes*

- Primary: adrenal tumour

- Secondary: pituitary ACTH-secreting tumour; ectopic ACTH production
- Iatrogenic: exogenous administration of steroids

### *Clinical features*

- Obesity – central distribution of fat – buffalo hump
- Purple striae
- Hypertension
- Osteoporosis
- Hypogonadism
- Growth failure
- Muscle wasting/hypotonia

### *Investigations*

- 24-h urine cortisol
- 24-h profile (loss of circadian rhythm, no suppression of midnight cortisol level)
- Dexamethasone suppression test
- MRI of the brain/CT of the adrenals

## **Congenital adrenal hyperplasia**

CAH describes the deficiency of one of the enzymes in the biosynthetic pathway of the adrenal cortex. The classic type is deficiency of the enzyme 21-hydroxylase.

### *Genetics*

Two genes encoding 21-hydroxylase expression have been localized to the short arm of chromosome 6, namely *CYP21B* and *CYP21A*. Deletion of *CYP21B* is associated with severe salt wasting and HLA-B47, -DR7 haplotype.

### *Pathophysiology*

In classic CAH, there is a block in the production of cortisol and aldosterone with a build-up of 17-hydroxyprogesterone, the precursor before the block. The continuing ACTH drive leads to the precursors being directed along the androgen biosynthetic pathway, causing virilization.

### *Presentation*

- Ambiguous genitalia (in girls with 21-hydroxylase deficiency, and occasionally in boys with 3 $\beta$ -hydroxy-steroid dehydrogenase deficiency)
- Salt-losing crisis and hypotension
- Hypertension may occur in 11 $\beta$ -hydroxylase deficiency
- Precocious puberty (in boys)
- Virilization

### *Investigation*

- Karyotype
- 17-Hydroxyprogesterone (17-OHP)
- Urine steroid profile (metabolite pattern will help in diagnosing specific enzyme block)
- Adrenal androgen levels

- Bone age in older children

### *Treatment*

Hydrocortisone and fludrocortisone replace the deficient steroids and also suppress the ACTH drive to the adrenal androgens. Growth is a good method of monitoring replacement therapy. Children who grow excessively fast with increased height velocity either are getting inadequate doses or may be non-compliant. 17-OHP levels are also useful for monitoring treatment.

- It is important to teach parents to recognize signs of illness and to be able to administer emergency hydrocortisone
- Additional sodium chloride replacement is also required during the first year of life and electrolytes may need to be monitored over this period
- Surgery may be required in girls with virilization

### *Side effects of glucocorticoid treatment*

When glucocorticoids are used in non-physiological doses such as in asthma, chronic renal failure or rheumatological and Immunological conditions, the following side effects may be seen:

- Gastritis
- Osteoporosis
- Raised blood glucose/altered glucose tolerance
- Increased appetite and weight gain
- Increased susceptibility to infection
- Poor healing
- Menstrual irregularities
- Unpredictable mood changes
- Sleep disturbances
- Increased risk of glaucoma and cataracts

## **6. THE THYROID GLAND**

### **6.1 Anatomy**

The thyroid gland is formed from a midline outpouching of ectoderm of the primitive buccal cavity, which then migrates caudally. It consists of follicles made of colloid surrounded by follicular cells and basement membrane. Thyroid hormone is synthesized at a cellular level and stored in thyroglobulin, a glycoprotein that is the main constituent of the colloid. Between the follicular cells are the parafollicular cells (C-cells), which are of neurogenic origin and secrete calcitonin.

### **6.2 Physiology**

The function of the thyroid gland is to concentrate iodine from the blood and return it to peripheral

tissues in the form of thyroid hormones (thyroxine or tetraiodothyronine [ $T_4$ ] and triiodothyronine [ $T_3$ ]). In blood, the hormones are linked with carrier proteins, e.g. thyroxine-binding globulin and pre-albumin.  $T_4$  is metabolized in the periphery into  $T_3$  (more potent) and reverse  $T_3$  (less potent).

## Hormonogenesis

Steps include:

1. Follicular cells actively uptake and tap iodine from the blood
2. Synthesis of thyroglobulin
3. Organification of trapped iodine as iodotyrosines (monoiodotyrosine [MIT] and diiodotyrosine [DIT])
4. Coupling of iodotyrosines to form iodothyronines and storage in the follicular colloid
5. Endocytosis of colloid droplets and hydrolysis of thyroglobulin to release  $T_3$ ,  $T_4$  and MIT and DIT
6. Deiodination of MIT and DIT with intrathyroid recycling of the iodine

Thyroid hormone acts by penetrating binding to a specific nuclear receptor. It modulates gene transcription and mRNA synthesis which leads to increased mitochondrial activity

## 6.3 Regulation

Thyroid hormone release is regulated by TSH and iodine levels. TSH has both immediate and delayed actions on thyroid hormone secretion.

- Immediate actions:
  - Stimulates binding of iodide to protein
  - Stimulates thyroid hormone release
  - Stimulates pathways of intermediate metabolism
- Delayed action (several hours):
  - Stimulates trapping of iodide
  - Stimulates synthesis of thyroglobulin

Physiological variations in iodide modulate trapping by the thyroid membrane.

Iodide inhibits the stimulation of cAMP by TSH and pharmacological doses block organification.

## 6.4 Functions of thyroid hormone

Thyroid hormone has multiple physiological actions as follows:

- Growth and development (required for somatic and neuronal growth)
- Thermogenesis

- Catabolism (increased glycogenolysis, lipolysis and free fatty acid oxidation)
- It also potentiates the actions of catecholamines

## 6.5 Investigation and management of thyroid disorders

- Baseline blood tests: free  $T_4$ / $T_3$ /TSH measurements
- Stimulation tests: TRH test
- Thyroid ultrasound scan
- Radionuclide scans

In primary hypothyroidism,  $T_4$  will be low and associated with a raised TSH. In hyperthyroidism,  $T_4$  will be raised and TSH suppressed.

In secondary hypothyroidism,  $T_4$  will be low in association with a low TSH. Further investigation is with a TRH test. This involves the injection of TRH followed by measurement of TSH at 30 and 60 min post-dose. In an individual with normal thyroid function, TSH would rise at 30 min but fall by 60 min. However, in patients with hypothalamic dysfunction, TSH would continue to rise at 60 min post-injection.

‘Sick thyroid syndrome’ refers to the scenario of a variety of abnormalities on thyroid function testing in an unwell patient that spontaneously resolve as the illness improves. Usually there is a normal free  $T_4$  level with raised TSH.

Thyroid ultrasound scans can identify nodules or cysts. Functional assessment can be made using the technetium radionuclides. Uptake is increased in thyrotoxicosis and reduced in thyroiditis. Furthermore, it may reveal a ‘cold’ nodule which might be suggestive of malignancy.

## 6.6 Disorders of thyroid function

### Hypothyroidism

Hypothyroidism may be primary (thyroid gland) or secondary (central). Furthermore it may be congenital or acquired. However, the most common cause of thyroid dysfunction is iodine deficiency disorder (IDD). Salt iodization has proven a cost-effective solution.

### Primary hypothyroidism

- Congenital:
  - Thyroid dysgenesis
  - Agenesis
  - Hypoplasia
  - Ectopic gland
  - Biosynthetic defects



- Maternal thyroid disorder
- Acquired:
  - Autoimmune
  - Post-surgery
  - Post-cervical irradiation
  - Systemic disorders
  - Iodine deficiency
  - Iodine overload

## Secondary hypothyroidism

- Congenital:
  - Congenital pituitary abnormalities
  - Receptor resistance
- Acquired:
  - Post-cranial irradiation
  - Post-tumour
  - Post-surgery

Congenital hypothyroidism has an incidence of 1/4000 live births. Most cases of thyroid dysgenesis are sporadic. The TSH receptor is critical for gland development and inactivating mutations may cause a range of severity of hypothyroidism. An activation mutation in *GNAS1* causes McCune–Albright syndrome. Thyroid dysmorphogenesis has an autosomal recessive inheritance and mutations of *SLC26A4* cause Pendred syndrome. Transient congenital hypothyroidism may be due to maternal anti-TSH antibodies or heterozygous *DUOX2* mutations.

The most common cause of acquired hypothyroidism is autoimmune.

### Screening for congenital hypothyroidism

TSH is measured as part of the newborn screening programme performed between days 5 and 7 of life. A blood spot from a heel prick is put on to a filter paper. Concentrations of TSH >10 mU/l are picked up by this test and abnormal results are immediately notified by the test centre to the relevant local hospital/specialist unit or the GP.

This screening programme detects >90% of cases of congenital hypothyroidism. Those due to secondary (pituitary causes) are picked up as TSH levels are low.

It is essential that treatment with oral thyroxine is started as soon as the definitive measurements of TSH and free T<sub>4</sub> have been performed because delay may lead to a lower IQ and affect psychomotor development.

### Management of hypothyroidism

Treatment is with L-thyroxine and is monitored by regular measurements of free T<sub>4</sub> and TSH.

# Hyperthyroidism

Thyrotoxicosis is uncommon in childhood but rises to 3/100 000 in adolescence with a female:male ratio of 8:1; 95% of young people with thyrotoxicosis have Graves disease which is caused by stimulatory antibodies to the TSH receptor. This is a multisystem disorder affecting the skin, eyes and thyroid gland. Very rarely a monogenic cause is found caused by activating mutations in the TSH receptor gene or *GNAS1*.

## Causes of thyrotoxicosis

- Autoimmune thyroiditis, e.g. Graves disease
- Diffuse toxic goitre
- Nodular toxic goitre
- TSH induced
- Factitious

Neonatal thyrotoxicosis is a rare condition caused by the transplacental passage of thyroid-stimulating antibodies from mothers with either Graves disease (active or inactive) or Hashimoto thyroiditis. The neonate usually presents with a rapidly developing tachycardia, dysrhythmia, hypertension and weight loss. A goitre may be present. There may also be associated jaundice and thrombocytopenia. The condition is usually self-limiting in 4–12 weeks but severely affected neonates will require treatment with propranolol, carbamazepine and Lugol's iodine. A response is usually seen within 24–36 hours.

## Thyroid neoplasia

This usually presents as solitary nodules, of which 50% are benign adenomas or cystic lesions. The prevalence of malignancy in childhood is 30–40% and the risk increases following radiation to the neck during infancy or early childhood. Hyperfunctioning adenomas are rare and most (90%) are well-differentiated follicular carcinomas.

Medullary carcinoma may occur as part of the MEN II (hyperparathyroidism and pheochromocytoma) syndrome.

## Management of hyperthyroidism

- Initial medical treatment:
  - Suppression of thyroid hormone secretion using specific antithyroid treatments, e.g. carbimazole, propylthiouracil
  - Blunting the peripheral effects of the thyroid hormones using  $\alpha$  blockade, e.g. propranolol
- Definitive treatment:
  - This is contemplated if there has been no remission in symptoms on medical treatment, and may involve subtotal thyroidectomy or radioactive iodine, which is becoming an increasingly popular choice for teenagers. The mortality rate is 1/1000 for thyroidectomies and morbidity includes recurrent laryngeal nerve damage and hypoparathyroidism

## 7. DIABETES AND HYPOGLYCAEMIA

### 7.1 Physiology of glucose homeostasis

The concentration of glucose in the blood is maintained by a balance between food intake or glucose mobilization from the liver and glucose utilization. Homeostatic mechanisms keep this within a narrow range.

In the fed state, insulin release is stimulated by a raised glucose and amino acid concentration. It is also stimulated by gut hormone release. In the fasting state, blood glucose concentrations fall and insulin production is turned off under the influence of somatostatin. A low glucose concentration is sensed by the hypothalamus, which regulates pancreatic secretion and stimulates the release of the counter-regulatory hormones glucagon, ACTH, GH, prolactin and catecholamines.

#### **Actions of insulin**

- Liver:
  - Conversion of glucose to glycogen
  - Inhibits gluconeogenesis
  - Inhibits glycogenolysis
- Peripheral:
  - Stimulates glucose and amino acid uptake by muscle
  - Stimulates glucose uptake by fat cells to form triglycerides

#### **Actions of the counter-regulatory hormones**

- Inhibition of glucose uptake
- Stimulation of amino acid release by muscle
- Stimulation of lipolysis to release free fatty acids which can be oxidized to form ketones
- Stimulation of gluconeogenesis and glycogenolysis

### 7.2 Diabetes mellitus

#### **Definition**

The World Health Organization (WHO), in its 2006 publication, defines diabetes as a fasting blood  $>7$  mmol/l or a blood glucose 2 h after a glucose load  $>11.1$  mmol/. In 2011 an addendum to these diagnostic criteria was added as a glycated haemoglobin (HbA1c) of  $>6.5\%$ . A glucose tolerance test is not routinely necessary for the diagnosis.

#### **Epidemiology**

The UK annual incidence is 20 per 100 000 children. Many countries report a rising incidence, particularly in children <5 years of age. Peaks occur at age 4–6 years and 10–14 years. There is no clear pattern of inheritance but there is an increased risk if a family member is affected. A person has a 10% risk of developing type 1 diabetes mellitus if they have an affected sibling.

## **Aetiology of diabetes in children**

- Type 1 diabetes mellitus (95%):
  - Autoimmune destruction of the pancreatic islet cells
- Type 2 diabetes mellitus:
  - A combination of  $\beta$ -cell failure and insulin resistance
- Cystic fibrosis-related diabetes
- Maturity-onset diabetes of the young (MODY)
- Genetic syndromes (Down syndrome, Wolfram syndrome, DIDMOAD and neonatal diabetes)

The most common type of diabetes in childhood is type 1.

## **Risk factors for type 2 diabetes**

- Family history of type 2 diabetes
- High-risk ethnic groups (African, Caribbean, Asian, Hispanic)
- Obesity
- Female sex
- Clinical signs of insulin resistance (acanthosis nigricans, POS)
- Biochemical signs of insulin resistance (high insulin or C-peptide)
- Pubertal
- Absence of islet cell antibodies

## **Physiology of diabetes in $\beta$ -cell failure in type 1 diabetes mellitus**

Low insulin level ultimately leads to ketoacidosis through the following mechanisms:

- Liver glycogen mobilization to form glucose
- Muscle protein breakdown to form free amino acids
- Adipose tissue breakdown of triglycerides to form free fatty acids which are oxidized to form ketone bodies

As the blood glucose level increases, the glucose in the glomerular filtrate exceeds the ability of the proximal tubules to reabsorb it. This leads to glycosuria. Polyuria then occurs, as the loop of Henle is unable to concentrate the urine because the renal tubules are insufficiently hyperosmolar. Extracellular volume depletion leads to thirst and polydipsia.

## **Differential diagnosis of polyuria and polydipsia**

- Diabetes mellitus
- Diabetes insipidus:
  - Cranial – arginine vasopressin deficiency
  - Nephrogenic – AVP insensitivity
- Habitual water drinking
- Drug induced

## **Presentation of childhood diabetes**

Children usually present acutely with polyuria (including nocturia and incontinence), thirst, polydipsia. About 40% have diabetic ketoacidosis. Other symptoms are weight loss, fatigue, infections (e.g. abscess formation, urinary tract infections), muscle cramps and abdominal pain.

## **Management of a child with newly diagnosed diabetes**

In 2004 NICE published specific guidance on the management of type 1 diabetes in children and young people. Diabetic ketoacidosis (DKA) is the most common presentation of type 1 diabetes and the most common cause of diabetes-related death in children.

## **Diabetic ketoacidosis**

DKA is defined as:

- hyperglycaemia (glucose  $>11$  mmol/l)
- pH  $<7.3$
- bicarbonate  $<15$  mmol/l

and patients who are:

- 5% or more dehydrated
- and/or vomiting
- and/or drowsy
- and/or clinically acidotic

National guidelines were published in 2009 by the British Society of Paediatric Endocrinology and Diabetes for the management of DKA.

## **Principles of management of DKA**

### *General resuscitation*

If there is evidence of shock (tachycardia, poor peripheral pulses, poor capillary refill and /or hypotension) then give 10 ml/kg of 0.9% saline and repeat as necessary to a maximum of 30 ml/kg.

### *Confirm the diagnosis*

This is confirmed by clinical assessment, capillary blood glucose testing, blood gas and urine or blood ketone measurement.

### *Full clinical assessment*

This should include an assessment of dehydration and conscious level.

### *Fluid management*

$$\text{Requirement} = \text{Maintenance} + \text{Deficit} \\ - \text{Fluid already given}$$

## **Maintenance requirements:**

Weight	Fluid requirement
0–12.9 kg	80 ml/kg per 24 h
13–19.9 kg	55 ml/kg per 24 h
35–59.9 kg	45 ml/kg per 24 h
(>60 kg)	35 ml/kg per 24 h

$$\text{Deficit (litres)} = \text{Percentage dehydration} \times \text{Bodyweight (kg)}$$

For most children, use 5–8% dehydration to calculate fluids.

$$\text{Hourly rate} = [48 \text{ h maintenance} + \text{Deficit} - \text{Resuscitation fluid already given}] / 48$$

Initially use 0.9% saline with 20 mmol KCl in 500 ml, and continue this sodium concentration for at least 12 hours. Once the blood glucose has fallen to 14 mmol/l add glucose to the fluid. After 12 h, if the plasma sodium level is stable or increasing, change to 500 ml bags of 0.45% saline/5% glucose/20 mmol KCl. If the plasma sodium is falling, continue with 0.9% saline

### *Insulin*

DO NOT start insulin until intravenous fluids have been running for at least an hour. The insulin solution should then run at 0.1 units/kg per hour. For children who are already on long-acting insulin you may want this to continue at the usual dose and time throughout the DKA treatment, in addition to the intravenous insulin infusion, in order to shorten length of stay after recovery from DKA.

### **Cerebral oedema**

The signs and symptoms of cerebral oedema include:

- Headache and slowing of heart rate
- Change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
- Specific neurological signs (e.g. cranial nerve palsies)

- Rising BP, decreased O<sub>2</sub> saturation
- Abnormal posturing

The following measures should be taken immediately while arranging transfer to the paediatric intensive care unit (PICU):

- Exclude hypoglycaemia as a possible cause of any behaviour change
- Give hypertonic (2.7%) saline (5 ml/kg over 5–10 min) or mannitol 0.5–1.0 g/kg stat (= 2.5–5 ml/kg mannitol 20% over 20 min)
- Restrict intravenous fluids to 1/2 maintenance and replace deficit over 72 rather than 48 h
- The child will need to be moved to PICU (if not there already)
- Discuss intubation with PICU consultant

### **Long-term management of diabetes**

Children and young people with type 1 diabetes should be offered an ongoing integrated package of care by a multidisciplinary paediatric diabetes care team.

The target for long-term glycaemic control is an HbA1c level <7.5% (to minimize the risk of long-term complications) without frequent disabling hypoglycaemia.

Children and young people with type 1 diabetes should be offered screening for the following:

- Coeliac disease at diagnosis and at least every 3 years thereafter until transfer to adult services
- Thyroid disease at diagnosis and annually thereafter until transfer to adult services
- Retinopathy annually from the age of 12 years
- Microalbuminuria annually from the age of 12 years
- Blood pressure annually from the age of 12 years

### **Insulin regimens**

#### *One, two or three insulin injections per day*

These are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin.

#### *Multiple daily injection regimen*

The person has injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue.

#### *Continuous subcutaneous insulin infusion*

A programmable pump and insulin storage reservoir attached to a subcutaneous needle or cannula give a continuous amount of rapid-acting insulin analogue as basal insulin and via which bolus insulin may be given.

### **Diet**

The aim is for a healthy balanced diet. The intensive insulin regimens allow for a more flexible eating pattern because the rapid-acting insulin can be adjusted according to the carbohydrate content of individual meals. However, the twice-daily insulin regimen requires a consistency of meal times with regular snacks and consistent carbohydrate content of meals.

### **Exercise**

Exercise is important to maintain cardiovascular fitness but also reduces blood glucose levels.

### **Blood glucose testing**

Capillary blood glucose testing many times daily is essential to monitor glycaemic control and enables insulin dose adjustment. In addition continuous glucose monitoring systems are available.

### **Hypoglycaemia in a child on insulin treatment**

Hypoglycaemia in a person on glucose-lowering treatment is defined as a blood glucose  $<4$  mmol/l. The symptoms may be divided into neuroglycaemic and adrenergic, and include weakness, trembling, dizziness, poor concentration, hunger, sweating, pallor, aggressiveness, irritability and confusion.

The initial management of hypoglycaemia is to have refined sugar, e.g. glucose tablets, followed by a complex carbohydrate food, e.g. a biscuit or sandwich. If the hypoglycaemic child is unconscious or unable to cooperate with glucose administration orally, then intramuscular glucagon may be administered.

## **7.3 Hypoglycaemia**

### **Causes of hypoglycaemia**

- Inadequate glucose production:
  - Counter-regulatory hormone deficiencies
  - Glycogen storage disease
  - Enzyme deficiency, e.g. galactosaemia
- Excessive glucose consumption, i.e. hyperinsulinism:
  - Transient
  - Infant of a mother with diabetes
  - Beckwith–Wiedemann syndrome
- Persistent:
  - Persistent hyperinsulinaemic hypoglycaemia of infancy
  - Insulinoma
  - Exogenous insulin

### **Investigation of hypoglycaemia**

Blood taken for a diagnostic screen is useful only if taken when the patient is hypoglycaemic (glucose  $<2.6$  mmol/l) and should include the following:



- Blood:
  - Glucose
  - Insulin (C-peptide)
  - Cortisol
  - GH
  - Lactate
  - Free fatty acids
  - Amino acids
  - Ketone bodies ( $\beta$ -hydroxybutyrate and acetoacetate)
  - Acylcarnitines
- Urine:
  - Organic acids

In hypoglycaemic states in the absence of ketones it is important to look at the free fatty acids (FFAs). Normal FFAs suggest hyperinsulinism and raised FFAs a fatty-acid oxidation defect. Hypoglycaemia in the presence of urinary ketones suggests either a counter-regulatory hormone deficiency or an enzyme defect in the glycogenolysis or gluconeogenesis pathways.

(For further information please refer to Chapter 16.)

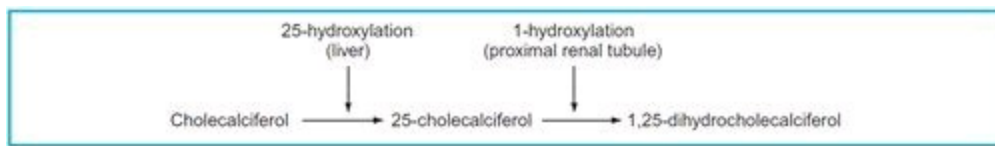
## 8. BONE METABOLISM

### 8.1 Physiology of calcium and phosphate homeostasis

- Principal regulators of calcium concentration:
  - Vitamin D (and its active metabolites)
  - PTH
  - Calcitonin
- Regulators of phosphate concentrations:
  - Main regulator is vitamin D
  - Less strictly controlled than calcium

### Vitamin D

Vitamin D<sub>3</sub> (cholecalciferol) is produced in the skin from a pro-vitamin as a result of exposure to ultraviolet light. Excess sunlight converts pro-vitamin D to an inactive compound, thus preventing vitamin D intoxication. Vitamin D is also ingested and is a fat-soluble vitamin. Vitamin D is converted to its active form by hydroxylation – initially to its 25-hydroxyl form in the liver and the subsequent 1,25-dihydroxylation occurs in the kidney.



## Vitamin D activation pathway

### Actions of vitamin D

- Increases intestinal absorption of calcium
- Increases osteoclastic bone resorption
- Inhibits PTH secretion and hence increases  $1\alpha$ -hydroxylation

There is some evidence to suggest the existence of a signalling pathway connecting bone and glucose metabolism, involving the hormones leptin, osteocalcin and adiponectin.

A position statement from the UK Scientific Advisory Committee on Nutrition 2007 concluded that a significant proportion of the UK population have a low vitamin D status. At-risk groups include infants, and people of south Asian and African–Caribbean ethnic origins.

### Parathyroid hormone

The *PTH* gene is located on chromosome 11. Active PTH is cleaved from a pro-hormone and then secreted by the parathyroid glands. Low calcium, cortisol, prolactin, phosphate and vitamin D all affect PTH secretion, but maximal PTH secretion occurs at a calcium concentration of  $<2$  mmol/l.

### Immediate effects of PTH

- Reduction in renal calcium excretion. It promotes calcium reabsorption in the distal tubule by stimulating the  $1\alpha$ -hydroxylation of vitamin D
- Promotion of phosphaturia by inhibiting phosphate and bicarbonate reabsorption in the proximal tubule
- Mobilization of calcium from bone – together with vitamin A, the osteoblasts are stimulated to produce a factor that activates osteoclasts to mobilize calcium
- Delayed effects of PTH
- Promotion of calcium and phosphate absorption from gut

### Calcitonin

This is produced by the C-cells of the thyroid gland and synthesized as a large precursor molecule. Its primary functions:

- It inhibits bone resorption
- It is thought to interact with GI hormones to prevent postprandial hypercalcaemia

## 8.2 Disorders of calcium and phosphate metabolism

### Hypocalcaemia

#### Causes of hypocalcaemia

- Transient neonatal hypocalcaemia
- Dietary
- Malabsorption
- Vitamin D deficiency
- Hypoparathyroidism
- Pseudohypoparathyroidism

### Hypoparathyroidism

#### Causes of hypoparathyroidism

- Parathyroid absence or aplasia
- DiGeorge syndrome (thymic abnormalities/cardiac defects/facial appearances)
- Autoimmune
- Associated with multiple endocrinopathy
- Iatrogenic – post-thyroid surgery

#### Treatment

In primary hypoparathyroidism, the management of neonatal tetany consists of intravenous calcium gluconate and oral 1,25-dihydroxycholecalciferol.

Subsequent management is with vitamin D and an adequate intake of calcium.

### Pseudohypoparathyroidism

#### Clinical features

- Learning disability
- Short stature
- Characteristic facies
- Shortening of fourth and fifth metacarpal and metatarsal
- Ectopic calcification

#### Aetiology

PHP types 1a and 1c result from heterozygous inactivating mutations of the  $\alpha$  subunit of the stimulatory G-protein (Gs). Both are associated with Albright hereditary osteodystrophy and, when the mutation is maternally derived, end-organ resistance to multiple hormones. Due to complex tissue

specific imprinting of  $Gsa$ , paternally derived mutations do not usually lead to hormone resistance resulting in the condition termed pseudo-pseudohypoparathyroidism. More than 100 mutations have been characterized in PHP-1 $\alpha$  with a mutational hotspot in exon 7.

## **Hypercalcaemia**

Clinical features are non-specific, often with anorexia, constipation, polyuria, nausea and vomiting in a child with failure to thrive.

### **Causes of hypercalcaemia**

- Low PTH:
  - Vitamin D intoxication
  - Infantile hypercalcaemia
  - Transient
  - Williams syndrome
  - Associated with tumours
- High PTH:
  - Primary hyperparathyroidism
  - Familial hypocalciuric hypercalcaemia

## **Rickets**

### **Causes of rickets**

- Hypocalcaemic:
  - Calcium deficiency:
    - Dietary
    - Malabsorption
  - Vitamin D deficiency:
    - Dietary
    - Malabsorption
    - Lack of sunlight
    - Liver disease
    - Anticonvulsants
    - Biosynthetic defect of vitamin D
    - 1 $\alpha$ -Hydroxylase deficiency
  - Defective vitamin D action
- Phosphopenic:
  - Renal tubular loss
    - Isolated, e.g. X-linked hypophosphataemia
    - Mixed tubular, e.g. Fanconi anaemia
- Abnormal bones
- Renal osteodystrophy

## 8.3 Investigation of bone abnormalities

- Calcium, phosphate, alkaline phosphatase
- Creatinine
- 1,25-Hydroxy-vitamin D, 25-hydroxy-vitamin D, vitamin D concentrations
- PTH
- Urinary calcium, phosphate, creatinine and cAMP
- X-rays
- DXA (dual-energy X-ray absorptiometry)

## 9. MISCELLANEOUS ENDOCRINE DISORDERS

### 9.1 Obesity

Obesity is an excessive accumulation of fat. This may be due to an increase in size or the number of adipocytes. There is no threshold value at which fatness becomes pathological.

#### Causes of obesity

- Nutritional:
  - Simple obesity/constitutional obesity
- Monogenic
- Associated with genetic syndromes:
  - Down syndrome
  - Laurence–Moon–Biedl syndrome
  - Prader–Willi syndrome
- Endocrine:
  - Hypothalamic damage
  - Hypopituitarism, GH deficiency
  - Hypogonadism
  - Hypothyroidism
  - Cushing syndrome
  - Pseudohypoparathyroidism
  - Hyperinsulinism
- Iatrogenic
  - Glucocorticoids
  - Oestrogens
- Inactivity
- Psychological disturbances

In general, simple constitutional obesity is associated with tall stature in childhood, whereas

endocrine causes of obesity tend to be associated with short stature or a reduction in height velocity.

Monogenic causes of obesity syndromes are characterized by normal birthweights, followed by a rapid weight gain in the first few months of life. The obesity is primarily truncal and limb in distribution and is associated with intense food-seeking behaviour. This leads to hyperinsulinism and a high risk in adulthood of type 2 diabetes. The main monogenic forms of obesity identified are mutations in the leptin gene (or receptor gene), the POMC gene and *MC4R* (melanocortin receptor).

## **Consequences of obesity**

### **Childhood**

- Insulin resistance and abnormal glucose tolerance
- Type 2 diabetes
- Non-alcoholic steatohepatitis
- Psychological problems
- Obstructive sleep apnoea
- Increased cardiac diameter

### **Adulthood**

- Hyperlipidaemia
- Hypertension
- Diabetes
- Increased risk of death from cardiovascular disease

## **Syndromes associated with obesity**

### **Prader–Willi syndrome**

- Genetics: deletion from paternally derived long arm of chromosome 15q
- Clinical features:
  - Neonatal hypotonia
  - Feeding difficulties in the newborn period
  - Obesity (food-seeking behaviour)
  - Hypogonadism
  - Tendency to diabetes mellitus
  - Strabismus
  - Facial features:
    - Narrow forehead
    - Olive-shaped eyes
    - Anti-mongoloid slant
    - Carp mouth
    - Abnormal ear lobes

- Orthopaedic:
  - Small, tapering fingers
  - Congenital dislocation of the hips
  - Retarded bone age
- IQ: reduced, usually 40–70
- Behavioural difficulties: food seeking
- Endocrine: insulin resistance

## **Bardet–Biedl syndrome**

- Genetics
  - Mutations in at least 14 different genes have been identified. These genes often referred to as *BBS* genes, are involved in the structure and function of cilia
- Clinical features:
  - Learning disability
  - Obesity – marked by 4 years of age
  - Retinitis pigmentosa/strabismus
  - Polydactyly/clinodactyly
  - Moderate short stature
  - Hypogonadism
- Associations:
  - Renal abnormalities
  - Diabetes insipidus

## **Beckwith–Wiedemann syndrome**

- Genetics:
  - Usually occurs where there is abnormal regulation of genes in a particular region of chromosome 11. Up to 20% cases are due to paternal uniparental disomy
- Clinical features:
  - Large birthweight
  - Transient hyperinsulinism
  - Macrosomia
  - Linear fissures on ear lobes
  - Umbilical hernia/exomphalos
  - Hemihypertrophy
- Associations:
  - Wilms tumour

## **Assessment of the obese child**

- Height, weight and pubertal assessment
- Body mass index (BMI):  $BMI = \text{weight (kg)} / \text{height (m)}^2$ ; in children, the BMI should be compared with BMI centile charts for age as BMI varies during different phases of childhood.

- Identification of an underlying cause:
  - Thyroid function tests
  - Cortisol measurements
- Evidence of complications:
  - Respiratory function
  - Liver function tests
  - Orthopaedic problems
  - Blood pressure
  - Fasting lipids
  - Oral glucose tolerance test

## **Management of obesity**

- Identification and treatment of underlying cause
- Dietary measures
- Reduction in sedentary behaviour
- Increased exercise
- Psychological support

## **9.2 Multiple endocrine neoplasia syndromes**

### **Autosomal dominant syndromes:**

- Type I (Wermer syndrome): pancreatic (gastrinoma, insulinoma)/pituitary/parathyroid. This is caused by mutations in the *MEN1* gene which provides instructions for producing a protein called menin; this acts as a tumour suppressor
- Type II (Sipple syndrome): medullary thyroid cancer/parathyroid/phaeochromocytoma. This is caused by mutations in the *RET* gene which provides instructions for a protein involved with signalling within cells

Patients with MEN IIb have additional phenotypic features – marfanoid habitus, skeletal abnormalities, abnormal dental enamel, multiple mucosal neuromas.

## **9.3 Autoimmune polyglandular syndromes**

- Type 1: Addison disease, chronic mucocutaneous candidiasis, hypoparathyroidism
- Type 2: primary hypothyroidism, primary hypogonadism, type 1 diabetes, pernicious anaemia, Addison disease, vitiligo

## **9.4 Endocrine complications of other disorders**



The endocrine glands may be affected by other chronic illnesses or their management regimens:

- Chronic pancreatitis
- Cystic fibrosis-related diabetes
- Exogenous steroids (adrenal suppression/diabetes)
- Tumours – local erosion, radiotherapy, chemotherapy, surgical excision
- Thalassaemia (e.g. secondary iron overload due to multiple blood transfusions)

## 9.5 Disorders of sexual development

### Classification

#### Virilized female

- Inadequately virilized male
- True hermaphrodite

#### *Causes of a virilized female*

- Androgens of fetal origin
- CAH
- Androgens of maternal origin
- Drugs/maternal CAH
- Tumours of ovary or adrenal gland
- Idiopathic

#### Causes of an inadequately virilized male

- XY gonadal dysgenesis
- LH deficiency: Leydig cell hypoplasia
- Inborn errors of testosterone synthesis
- 5 $\alpha$ -Reductase deficiency
- Androgen insensitivity

### Useful investigations

- Karyotype
- Urine steroid profile
- Pelvic ultrasonography
- 17-Hydroxyprogesterone (day 3)
- LH/FSH or testosterone/dihydrotestosterone
- Human chorionic gonadotrophin (hCG) test

Management of a child with a disorder of sexual development requires multidisciplinary assessment

and management involving endocrinology, paediatric urology, gynaecology and psychology input.

## 9.6 Amenorrhoea

### Causes of amenorrhoea

#### Ovarian

- Gonadal dysfunction
- Secondary to irradiation/chemotherapy/surgery
- Polycystic ovarian syndrome

#### Genital tract

- Müllerian dysgenesis
- Hypothalamopituitary
- Hypogonadotropic hypogonadism
- Secondary to tumours/irradiation/chemotherapy/surgery

#### Functional

- Weight loss
- Exercise induced
- Chronic illness
- Psychogenic

### Management of amenorrhoea

Management of amenorrhoea depends on the underlying cause. Structural abnormalities may need surgical correction. Primary amenorrhoea may require pubertal induction with exogenous oestrogen. In secondary amenorrhoea the underlying cause needs to be identified and addressed.

## 10. FURTHER READING

Brook CGD, Hindmarsh PC, eds (2001). *Clinical Paediatric Endocrinology*, 4th edn. Oxford: Blackwell Science.

Diabetes Control and Complications Trial Research Group (1994). Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* **125**:177–188.

Hindmarsh PC (2002). Optimization of thyroxine dose in congenital hypothyroidism. *Arch Dis Childh*

National Institute for Health and Clinical Excellence (2004). *Type 1 Diabetes: Diagnosis and management of Type 1 diabetes in children and young people*. London: NICE.

World Health Organization (2006). *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia*. Geneva: WHO.

World Health Organization (2011). *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus*. Geneva: WHO.

---

# Chapter 9

## Ethics and Law

*Vic Larcher and Robert Wheeler*

---

## CONTENTS

### Ethics

#### 1. Ethical issues, technology and law

#### 2. Moral theories and principles

2.1 Consequentialism/Utilitarian moral theory

2.2 Deontology

2.3 Virtue ethics

2.4 Principles

#### 3. Moral analysis of cases and issues

3.1 Moral duties of doctors

3.2 Moral conflicts for doctors

3.3 Best interests

#### 4. Moral theory and moral status of children

4.1 Children's autonomy

#### 5. Parental responsibilities, rights, duties and powers

#### 6. Children's rights

6.1 Key principles of UN Convention

#### 7. Withholding or withdrawing life-sustaining treatment

7.1 The legal framework for withholding or withdrawing life-sustaining treatment

7.2 Professional guidance

[7.3 The process of decision-making](#)

[7.4 Managing disputes/dissent](#)

[7.5 The extremely preterm infant \(<24 weeks' gestation\)](#)

## **[8. Consent \(ethical basis\)](#)**

## **[9. Confidentiality](#)**

[9.1 Confidentiality and children](#)

[9.2 Confidentiality and child protection](#)

## **[10. Contraception, consent and confidentiality in teenagers](#)**

## **[11. Abortion](#)**

## **[12. Research in children](#)**

## **[13. Ethics and law](#)**

## **[Child Law](#)**

## **[14. An introduction](#)**

## **[15. Children Act 1989](#)**

## **[16. What is a child?](#)**

[16.1 'Full legal capacity'](#)

## **[17. Status in courts](#)**

## **[18. Who 'owns' the child?](#)**

[18.1 Children Act 1989](#)

[18.2 Parental responsibility](#)

[18.3 Wardship](#)

[18.4 Guardians](#)

## **[19. Consent](#)**

## **[20. Children's capacity](#)**

[20.1 16–17 years](#)

[20.2 Preschool](#)

[20.3 The intervening years: Gillick competence](#)

[20.4 Fraser Guidelines](#)

## **21. Further reading**

---

# Ethics

---

## 1. ETHICAL ISSUES, TECHNOLOGY AND LAW

The purpose of this chapter is to provide an account of the ethical principles that underpin good clinical paediatric practice and of the law as it relates to children in the UK. A knowledge of ethical principles will help trainees in the analysis of ethical dilemmas that may arise in clinical practice and hopefully improve their resolution. It is important that ethical principles are applied in a way that is consistent with the law.

Ethical and legal dilemmas arise more frequently in paediatric practice than in adult medicine because of the perceived vulnerable status of children and the unique ethical and legal status that their parents have with respect to them. Parents have an ethical and legal duty to make decisions for children who lack the capacity to do so, while protecting them from harm and acting in their best interests. These duties may themselves conflict; parental perceptions of their duties and their child's needs may also lead to disagreements with professionals.

Contemporary paediatric practice may demand the application of advanced technology, the availability of which defines what **can** be done. It does not follow that what **can** be done **should** be done. Ethical dilemmas arise when appeal to clinical or scientific facts cannot determine what **should** be done, when ethical principles appear to conflict or when those involved, e.g. parents and clinicians, do not appear to share the same values. Their resolution involves value judgements that need to be reasonable, transparent, accountable and based on sound ethical principles or theory; there may be more than one 'right' answer. Such judgements must also conform to the law. Although the law is based on ethical principles, it has a different and more prescriptive function in decreeing what **must or must not** be done.

## 2. MORAL THEORIES AND PRINCIPLES

A moral philosopher's approach to dilemmas involves the application of classical moral theories or principles to deduce whether a proposed course of action is morally acceptable. In understanding this process some basic awareness of relevant moral theories and principles together with their strengths and weaknesses is helpful.

## 2.1 Consequentialism/Utilitarian moral theory

In consequentialism, the rightness or wrongness of an action is determined by its actual or foreseeable consequences. Utilitarianism is a type of consequentialism in which the best consequences are those in which happiness is maximized and harms are minimized for all relevant persons involved. An action is therefore morally correct if it maximizes welfare or individual preferences – ‘the greatest good for the greatest number’. Application of utilitarian moral theory requires calculation of risks/benefits and as such it underpins reflective, evidence-based, audited practice.

### Strengths of utilitarianism

- Consequences of actions do matter
- Appears to provide a clear answer as to what an individual should do
- Egalitarian, because everyone involved counts equally
- Satisfies aspirations, in that it promotes a happy society

### Weaknesses of utilitarianism

- Difficult to predict consequences with precision
- No universally agreed single measure of the components of the utilitarian calculus
- Some actions are wrong, even if they lead to best consequences, e.g. use of torture to gain information to prevent harm
- Maximizing happiness of the majority may be unjust to the minority, especially those who are weak and vulnerable and those who lack capacity
- Which counts more – intensity or length of happiness?

Application of the principle of utility requires a potentially difficult calculation of the effects of uncertain consequences, but this is so for many other decisions that involve balancing values. Some calculation of harms/benefits is routinely required in medicine, e.g. in distribution of health care to populations, or in allocation of scarce resources.

## 2.2 Deontology

According to deontological theory to be moral is to do one’s duty, or intend to do it, regardless of the consequences. This involves obeying moral rules, which can be derived by rational consideration or discovery, in the same way that natural laws, e.g. the laws of gravity or motion, can be deduced from physical events. Moral rules are universal (apply to everyone), unconditional (no exceptions) and imperative (obligatory or absolutely necessary). Some obligations are right regardless of consequences, e.g. truth telling, avoidance of harm to others.

Moral individuals should be rational (capable of discerning rules), able to formulate and carry out plans and govern their own conduct, and be free to do so (autonomous). Such individuals have their



own intrinsic value and should be respected. In particular they should not be used to further the ends of others (however praiseworthy) without their express consent. Although it is not clear as to the extent to which children and young people are to be considered as rational and autonomous, it is clear that they are owed *some* respect.

## **Strengths of deontology**

- General belief that some actions are wrong irrespective of consequences
- Upholds dignity and intrinsic value of individual
- Rational and supports equality
- ‘Do as you would be done by’

## **Weaknesses of deontology**

- Impossibility of truly free decisions – ‘Autonomy is a philosopher’s myth’
- Absolutist, austere, no place for duty of beneficence (obligation to benefit patients by acting in their best interests)
- Consequences do matter at times
- What if duties conflict? For example, the duties to avoid harm and tell the truth

Deciding between competing moral duties is difficult without taking some account of the consequences or likely consequences of actions.

## **2.3 Virtue ethics**

In virtue ethics an action is right if it is what a virtuous person (clinician) would do in similar circumstances. A virtuous person is one who exhibits the human character traits (virtues) that are required for the best life overall (flourishing). It is associated with a deeper sense of happiness or wellbeing than that described by utilitarianism. Although ostensibly concerned with personal flourishing many of the virtues, e.g. kindness, generosity and tolerance, are not intrinsically selfish.

## **Strengths of virtue ethics**

- It seems intuitively right to consider character in assessing right and wrong
- Explains why we might treat some people, e.g. family, differently
- Provides a richer moral vocabulary than other theories
- Pluralistic – employing values that other theories ignore
- Encourages clinicians to develop moral characters that make them good doctors

## **Weaknesses of virtue ethics**

- Virtue ethics is based on the concept of flourishing which is (1) hard to analyse and (2) insufficiently independent of other moral theories

- Fundamentally egocentric
- May not provide a separate helpful analytical framework for addressing moral dilemmas
- May be too conservative, tied to cultural norms

## 2.4 Principles

A more practical day-to-day approach is the application of moral principles that are compatible with or endorsed by a wide range of moral theories. Use of such principles is intended to transcend religious, cultural and philosophical differences.

When faced with an ethical dilemma it may be helpful to apply the following four moral principles that set out prima facie moral duties. When there is conflict between obligations or duties the prima facie obligation is the one that it seems morally more important to follow. The principles are:

- **Respect for autonomy** – this entails respecting the rights of patients to exercise as much self-determination as they are capable of. It involves giving sufficient information to permit informed choice and a duty to respect decisions of autonomous patients even when they conflict with those of professionals
- **Beneficence** – an obligation to benefit patients by acting in their best interests, e.g. by providing treatments that are intended to produce net clinical benefits. We do not usually have an obligation to benefit others, apart from those with whom we have special relationships, e.g. family and close friends. In contrast doctors do have duties, which are often referred to as superogatory to benefit their patients.
- **Non-maleficence** – an obligation not to cause net harm to patients even though some treatments may produce initial harm, e.g. chemotherapy. Applies to all, not just patients
- **Justice** – the obligation to act fairly and without discrimination, e.g. the distribution of health-care resources

### Strengths of principles approach

- Broad agreement that the four principles are valid and relevant
- Provides a moral checklist
- More flexible than moral theories
- More easily understood – easier to use

### Weaknesses of principles approach

- Questionable moral origin of the principles – no overarching moral theory
- No hierarchy of principles to resolve conflicts between them
- Do not provide solutions but a means of analysis
- Different cultures may place different emphasis on different principles – non-uniform approach
- Regarded by some as formulaic – ethics by numbers
- Scope – to whom or to what are duties owed and how widely do they apply?

The application of the four principles helps to clarify what ethical problems exist, but may not resolve dilemmas.

### 3. MORAL ANALYSIS OF CASES AND ISSUES

A moral philosopher's approach to dilemmas is essentially deductive. Clinicians tend to approach problems in a different fashion, working from the facts of a given case to the general medical/nursing principles that might apply.

Ethical examination of cases can follow this approach by starting from the features of the particular case and seeking to recall similar cases, which might help in resolving it. For example, in dealing with a 15 year old who is refusing further chemotherapy that his or her doctors recommend, we might examine how similar cases were resolved and what ethical principles were relevant to them.

An alternative 'four-quadrant' approach is to consider specific aspects of the case. These are (1) the clinical indicators or facts, e.g. prognosis, (2) the patient's preferences, (3) the quality of life that he or she has or will have and (4) contextual factors, e.g. parental views, and cultural and religious factors.

Whatever technique is used, arguments used to justify positions adopted should be fair and based on valid and sound reasoning. Emotional responses to dilemmas – 'the yuk factor' – cannot be discounted altogether because emotional responses may be morally important, moral intuitions have a role in moral reasoning and emotional responses to others are an essential component of the doctor–patient relationship. Nevertheless, such emotional responses require rational analysis and justification

#### 3.1 Moral duties of doctors

Doctors have a number of moral duties derived from application of theory and principle, namely:

- Preserve life, restore health and prevent disease
- Offer treatments that are intended to provide overall benefit and minimise harm
- Offer evidence-based treatment derived from ethically conducted research
- Respect the autonomy of their patients by respecting their right to as much self-determination as they are capable of
- Respect the human dignity of all patients regardless of their abilities
- Obtain appropriately informed voluntary consent
- Carry out the above duties fairly and justly and with appropriate skill and care
- Act within the framework provided by national and international law

### 3.2 Moral conflicts for doctors

From the above it follows that all medical interventions should be in the best interests of the patient and have their valid, freely given consent. The obligations to protect health and respect autonomy can and do conflict. In normal circumstances, the respect that is accorded to the principle of autonomy means that great importance is placed upon respecting the wishes, beliefs and preferences of those who are capable of expressing and acting upon them. Most adults are capable of making informed choices to accept or refuse treatment but children may lack this capacity. An important moral issue that arises in paediatric practice is what constitutes the best interests of a child and who should determine what they are.

### 3.3 Best interests

From a purely clinical perspective a treatment is in a child's best interests if it confers more clinical benefits than harms. This is a narrow view of best interests that may also be equated to welfare. Other considerations are important in coming to a wider view of best interests, including:

- The ascertainable wishes and feelings of the young person concerned, considered in the light of their age and understanding
- Physical, emotional, and educational needs
- Likely effect of change of circumstances on a young person's life
- Age, sex, cultural, religious and ethnic background
- Harm or risk of harm (physical, psychological, emotional, social, etc.)
- Capability of parents or others to meet the young person's needs

## 4. MORAL THEORY AND MORAL STATUS OF CHILDREN

As a result of the importance that we attach to respecting the worth of rational autonomous individuals, the moral status that we accord to children is important because it will determine how we should treat them. There are several views, namely:

- All children regardless of age have the same moral worth as adults
- All children are potential adults and should therefore be treated as such
- Society should grant children moral status because the consequences of doing so are better than treating them as though they have none
- Children's moral status depends on the extent to which they possess the qualities that we associate with personhood, e.g. consciousness, self-awareness, rationality, capacity for social interaction

The last approach accords with concepts of differing rates of growth and development with which paediatricians are familiar. It also seems an intuitive expression of respect for humanity to accord children more status than an animal with similar amounts of personhood-satisfying characteristics.

## 4.1 Children's autonomy

- Children vary enormously – as do adults – in their possession of personhood-satisfying characteristics
- Autonomy may be affected by illness, its treatments or moods
- Clinicians have a duty to enhance the development of as much autonomy as the child is capable of, e.g. by giving information and encouraging participation in decision-making
- Some children may not live long enough to develop autonomy, e.g. a child with aggressive glioblastoma
- Children may not achieve physical autonomy because of disability, e.g. muscular dystrophy
- Children may lack cognitive ability for self-determination, e.g. severe microcephaly, spastic quadriplegia
- Experience of illness may enhance autonomy, e.g. cystic fibrosis, Duchenne muscular dystrophy

## 5. PARENTAL RESPONSIBILITIES, RIGHTS, DUTIES AND POWERS

When children lack the capacity to make their own decisions, others have ethical and legal authority to act on their behalf. In most cultures, religions and legal systems parents have this responsibility (see Child law section). Parents also have moral obligations for their children's upbringing and for promotion and enhancement of their autonomy.

Application of both moral theory and law supports the autonomy of parents to rear their children in accordance with their own values provided that they act in the child's best interests and do not harm them.

A family's concept of their child's best interests is likely to be determined by a number of factors including:

- Their own ethical and value system
- Social, cultural and spiritual influences
- Religious beliefs
- Political and cultural attitudes
- Peer pressure, e.g. religious groups, neighbours
- Life experiences and outside influences, e.g. media reports

These may conflict with:

- Values of professionals from different socioeconomic backgrounds
- Children's need to make decisions that do not coincide with professional or parental choices

Conflicts may be exacerbated by:

- Power imbalances in professional–patient (child)–parent relationship

- Communication difficulties, e.g. language, understanding

## 6. CHILDREN’S RIGHTS

Rights are justifiable moral claims that confer obligations on others and may be derived from fundamental moral principles or form part of a social contract. They provide status and protection for individuals, especially those who lack capacity or rationality and enable others to seek redress on their behalf if rights are infringed. Rights may be positive or negative and may be defined by special relationships, e.g. parent–child.

Positive rights	Negative rights
Welfare, institutional and legal rights	Natural or liberty rights
Require action by others	Entail an obligation not to infringe
Established by social contract	Natural, Constant
Change as our society changes	Take precedence over positive rights
<i>Examples</i>	<i>Examples</i>
Rights to information and best available health care	Freedom of movement, speech, religious beliefs

The UN Convention of Rights of the Child applies to all aspects of a child’s life. The World Medical Association (WMA) has codified those rights pertaining to health. Both endorse the development of a rights-based, child-centred, health-care system.

### 6.1 Key principles of the UN Convention

- Any decision or action concerning children as individuals or a group must have their best interests as a primary consideration
- A child who is capable of forming his or her views has a right to express them freely
- A child’s view should be given due weight in accordance with that child’s age and maturity

Applied to medical practice this confers an obligation to consult children about treatment decisions and their implications, especially where cognitive ability is unimpaired, e.g. cystic fibrosis, cancer, renal failure and muscular dystrophy.

Other UN Convention articles affirm the right to:

- Freedom of expression (A13)
- The highest attainable standards of health care and rehabilitation from illness (A24)
- Privacy (A16)
- Freedom from discrimination (A2) and the right to family life and to hold religious beliefs

In addition, there are obligations to provide families with the necessary support, advice and services in caring for their children.

The WMA document emphasizes children's rights to:

- Child-centred health care
- Encouragement to achieve their full potential
- Choose how much they should be involved in decision-making and how much information they wish to receive
- Help and support in decision-making
- Delegation of decision-making to others
- Confidentiality
- An explanation of reasons why their preferences cannot be met

In considering a child's capacity to exercise his or her own rights it is important not to underestimate a child's capacity even though it clearly does not equate to an adult's. Parents, professionals or advocates may make decisions from an adult perspective and with a desire to protect children. These interventions may result in potential for personal choice being restricted, e.g. a teenage child with learning difficulties or muscular dystrophy who is prevented from mixing with the opposite sex. Some children may be unable to make a big choice, e.g. as to **whether** they will have a particular treatment, but they can decide **where** they will have it.

Individual rights may conflict, e.g. the right to life as opposed to freedom from inhuman and degrading treatment, as may rights possessed by various parties, e.g. children, parents, clinicians. A child's right not to be harmed takes precedence over the rights to family life when the latter cannot be maintained without abuse or neglect. Resources may not allow rights to be exercised in full. It is not clear whose rights take precedence and mere appeal to rights may be insufficient to protect children's interests.

## 7. WITHHOLDING OR WITHDRAWING LIFE-SUSTAINING TREATMENT

In most circumstances preserving a child's life is clearly in their best interests because treatment will be to their overall benefit. There may be circumstances in which this is not so, including:

- Life-limiting or life-shortening conditions for which there is no reasonable hope of cure or from which they will die
- Life-threatening conditions for which curative treatment may be feasible but can fail
- Children whose lives may be regarded as having limited value to the extent to which certain qualities, e.g. the capacity for meaningful social interaction, may be lacking or lessened

Life-sustaining treatments (LSTs) are those that have the potential to prolong life. They may include experimental therapies that are not validated by research as well as more conventional treatments such as cardiopulmonary resuscitation, mechanical ventilation, intravenous inotropes, antibiotics, renal dialysis, and clinically assisted nutrition and hydration. Evidence for burdens and benefits may



not always be available.

There are several different types of decision made about LST. Treatment that has not been commenced may be *withheld*. Alternatively, decisions may be made to *withdraw* treatment that has already started, or to impose *limits* on that treatment (e.g. to impose a maximum level of respiratory or cardiovascular support that will be provided).

The moral and legal justification for considering withholding, withdrawing or limiting LST must be that it is no longer in a child's best interests to continue to provide it.

There may be uncertainty about the likely prognosis for a small child with any given condition compounded by uncertainties about their potential for growth and development. In consequence children may receive more chances to revive from or survive their illnesses than comparable adults, with the imposition of greater burdens.

There must be a frank but sensitive discussion of the child's condition and prognosis, and a conscious decision to change the goals of treatment from cure to palliation. Palliative care for children and young people with life-limiting conditions is an active and total approach to care, from the point of diagnosis or recognition, throughout the child's life, death and beyond. It embraces physical, emotional, social and spiritual elements, and focuses on the enhancement of quality of life for the child/young person and support for the family. It includes the management of distressing symptoms, provision of short breaks and care through death and bereavement.

## 7.1 The legal framework for withholding or withdrawing LST

Deliberate killing is currently illegal and clinicians who deliberately act to shorten a child's life or take no action to save the life of patients whose death is foreseeable may face prosecution for murder or manslaughter.

The following principles are derived from specific judgments in individual cases in the UK. They clarify the circumstances in which withholding or withdrawing LST may be considered but do not provide legal sanction for individual future cases. If there is doubt or dispute in individual cases legal advice should *always* be sought

Courts have determined that the provision of LST is not in the best interests of patients in the following circumstances:

- Where an infant has such a 'demonstrably awful life' that no reasonable person would want to live
- Where death is imminent and irreversibly close, e.g. hydrocephalus and cerebral malformation
- Where the baby, although not close to death, had such severe disabilities that he would never be able to engage in any form of self-directed activity, e.g. severe spastic quadriplegia, with deafness, blindness and extremely limited capacity for interaction
- Where clinicians believe that LST is not in the best interests of the child, they cannot be forced to administer it even when the parents insist on it, e.g. severe brain damage as a consequence of



microcephaly and cerebral palsy. However, they may need to seek an alternative unit that will do so

- Permanent vegetative state, dependent on tube feeding for survival. The Court ruled that tube feeding was medical treatment and could be withdrawn because it was not in the best interests of the patient

Further judgements have determined:

- There is no legal distinction between withdrawing and withholding LST
- Non-provision of cardiopulmonary resuscitation is acceptable in circumstances of very severe brain damage
- Adults who are competent to do so may request that LST be withdrawn, especially if they face continuation of life that they regard as being worse than death

Requests for assisted suicide or active euthanasia continue to be rejected by English courts, despite attempts to change the law. It is unlikely that any legal authorisation of assisted dying will apply to children.

The legality of withdrawal of fluids from children who are not close to death or in a permanent vegetative state remains unclear and many professionals have ethical concerns about it.

Even considering UK Human Rights legislation, the courts appear to accept that there are circumstances in which the continued provision of LST no longer serves the broader concept of best interests.

## 7.2 Professional guidance

The Royal College of Paediatrics and Child Health (RCPCH) has published an ethical and legal framework within which decisions to withhold or withdraw LST might be made, and has provided advice on the process of decision-making and the resolution of conflicts. This document is currently under review but the RCPCH identified five situations in which withholding or withdrawing LST might be discussed. These were:

- Brain-stem death
- Permanent vegetative state
- The 'no chance' situation when LST only marginally delayed death without alleviating suffering
- The 'no purpose' situation when survival is possible but only at the cost of physical or mental impairment, which it would be unreasonable to expect the child to bear. It was envisaged that such children would never be capable of sufficient self-directed activity to make decisions for themselves (see legal criteria above)
- The intolerable situation where survival was again possible but, in the face of progressive and irreversible illness, the child and/or family believe that further treatment is more than the child and/or family can endure with any acceptable degree of human fulfilment. This situation clearly includes children with and without mental impairment

## 7.3 The process of decision-making

- All remediable causes for the child's condition must be excluded
- Absolute certainty over likely outcomes may not be possible and thus should be acknowledged
- There should be general acceptance that value judgements have to be made
- There should be openness and transparency in discussions within teams and with parents/children
- Consider second opinions to clarify the clinical position
- Formal ethics consultation may be helpful

## 7.4 Managing disputes/dissent

Disputes and dissent may arise within teams or with families as to what should be done. Where possible the reasons for this should be analysed so as to provide a means of resolution. Attention to or consideration of the following may be helpful:

- Communication
- Education/information sharing
- Negotiation/mediation/conciliation
- Trade offs, e.g. deferring to requests for benign treatment
- Consensus building
- Referral/second opinions
- Ethical review, e.g. clinical ethics committee
- Application to courts

## 7.5 The extremely preterm infant (<24 weeks' gestation)

In some countries neonatal intensive care may not be routinely offered to extremely preterm infants. In the UK there are guidelines for the management of babies according to gestational age and taking into account parental preferences and evidence available from outcome studies; it would not be recommended practice to resuscitate babies of under 22 weeks' gestation. If practicable, treatment options should be discussed with the family before the birth and decisions should be informed by the disclosure of both national, e.g. EPICURE 1 and 2, and local survival figures and complication rates.

Decisions to withhold or withdraw LST are often viewed as psychologically and emotionally distinct; withholding treatment may deprive a child of treatment from which they may potentially benefit.

If there is doubt concerning parental wishes or lack of senior paediatric support, the infant should be resuscitated and treated until a clearer picture of outcome emerges and parental views can be clarified.

Where disputes over the provision of LST cannot be settled by the above mechanisms a legal ruling on what is in the best interests of the child should be obtained before any action to withdraw LST.

## **Checklist for end of life decision-making**

Individuals may find the following checklist helpful in formulating end-of-life care plans and obtaining consent for them.

### **The child's clinical condition**

- Are sufficient and adequate medical facts available to make a diagnosis and give accurate prognosis?
- Has a potentially treatable condition been excluded?
- Is a second medical opinion necessary/desirable?
- Is there a need for a psychiatric or psychological assessment of the child?
- What are the problems in providing nursing care in the current situation?
- What are the views of nursing staff about changing goals for the child?
- What are the views of other therapists/professionals involved with the child?
- How has dissent in the team been handled?
- Is the child able to form a view about what he or she wants?
- Has he or she been consulted?

### **The family**

- Is the family's understanding of their child's condition adequate?
- What are the family's relevant religious and cultural beliefs and values?
- Has there been a psychosocial assessment of the family?
- What are the family's likely or actual views on changing goals of treatment?
- Do the family need the help of an advocate?

### **The decision-making process**

- How has uncertainty about the outcome been addressed?
- Has there been an ethical review of the case?
- Has there been a strategy meeting or psychosocial meeting?
- Have human rights issues been properly considered?
- Is there a proportionate justification for any infringement of human rights?
- Is there a need for a legal opinion?
- Is there a properly formulated care plan?
- Has informed consent for this care plan been obtained?
- Do the notes adequately reflect the process?
- How is the process to be maintained/audited?

## 8. CONSENT (ETHICAL BASIS)

The need to obtain consent for medical treatment is morally justified because it respects the rights of patients to make informed choices as to what will be done to them, respects their autonomy and avoids treating them merely as a means. It is likely to have good consequences for those involved. To be ethically valid, consent should be sufficiently informed, given by a person who has the capacity to understand the issues involved and obtained freely.

Children may have the legal capacity to give consent but, even if they do not, they still have the right to receive information given in a form and at a pace that they can comprehend.

Although it may be logical to suppose that a child who is competent to consent to treatment is also competent to refuse it – and should have that refusal honoured – this is not necessarily the law in England and Wales (see below). It may be that refusal to consent is not the same as a right to veto but this is ethically questionable. If a child's views are to be overridden they should receive an explanation as to why this will happen. It may be considered good practice to seek their assent, i.e. agreement, and where a treatment or intervention is not immediately necessary to delay it until they have had further opportunity to discuss it.

## 9. CONFIDENTIALITY

There is a general duty of confidentiality over the disclosure of personal information about patients (including children) to third parties.

In general such information should not be disclosed without the consent of the patient or those with parental responsibility in the case of children.

The ethical justifications for the above approach are:

- The obligation to respect children's autonomy and their right to exert control over their own personal data
- Confidentiality is a professional duty – implied promise not to disclose
- The duty of the virtuous doctor is to keep patient details confidential
- Better consequences follow if patients know that they can trust their doctors not to reveal information

General principles of confidentiality:

- Wherever possible consent for disclosure should be sought
- Data should be made anonymous if unidentifiable data will serve the purpose
- Only information necessary for the purpose in question should be disclosed
- Information can be shared within health-care teams, unless patients specifically object, because sharing of clinical and other information is implicit in and necessary for the effective delivery of health care

In general the law's approach to breaches of confidentiality is to consider whether there is a public interest in favour of breaching confidentiality or not breaching it.

Disclosure of information is a legal duty in certain circumstances:

- Notification of certain specified infectious diseases
- Notification of births and deaths
- If the court makes a specific request for it

Disclosure of information is discretionary in circumstances where:

- There is risk of significant harm to a third party
- It is necessary to do so for detection or prevention of serious crime including child abuse

## 9.1 Confidentiality and children

Children are owed the same duty of confidentiality as adults, irrespective of their legal status. The disclosure of information usually depends on the consent of the child or a person with parental responsibility.

Although children over 16 years are assumed to be competent to give consent, those under 16 may do so if they are able to understand what is involved and its consequences for their family (see Child law section). The principle that determines whether disclosure should take place is whether it is in the child's best interests to do so. Doctors may therefore ethically disclose information to parents of children younger than 18 years, even with the child's refusal, if they genuinely believe that it is in the young person's best interests to do so. This needs to be justified and the reasons for disclosure carefully explained.

## 9.2 Confidentiality and child protection

The paediatrician's primary duty is to the child not the carers. If a doctor has reasonable grounds to believe that a child is at risk of significant harm the facts should be reported to the appropriate statutory authority. Doctors have ethical and legal duties to assist statutory authorities in making relevant enquiries in such cases. They must satisfy themselves that disclosure of information is in the child's best interests. Information about competent children can be disclosed without their consent if to do so is justified on the above grounds. Information about non-competent children can be disclosed without parental consent if it is necessary to protect the child. The child and/or parents should normally be told about disclosure of information unless to do so would not be in the child's best interests or would expose them to risk of serious harm. All decisions about disclosure must be justifiable and reasonable.

## 10. CONTRACEPTION, CONSENT AND CONFIDENTIALITY IN TEENAGERS

Concern about teenage pregnancy rates stems from the ethical duty to protect children from harm. Ethical (and legal) dilemmas arise when children under the age of 16 years seek contraceptive advice without the express consent or knowledge of their parents and are adamant that their parents should not be informed.

Ethical justifications for respecting the young person's wishes are:

- The duty to respect their autonomous wishes
- The duty to confer more benefits than harms
- The adverse consequences of failing to provide confidential advice, e.g. increased pregnancy rates, sexually transmitted infections
- The respect for children's rights to health, information, identity

With respect to the legality of prescribing contraception to young people under the age of 16, it is clear that such children are considered to have the capacity to consent to medical treatment provided that they understand the nature and purpose of what is involved and its implications for themselves and their family.

The legal (Fraser's) criteria for the prescription of contraception (including emergency contraception) to adolescents are:

- Ability to understand implications for self and family
- There is a sustained and consistent refusal to discuss with parents
- The young person has made a decision to start or continue to have sexual intercourse, despite attempts at persuasion
- The adolescent's health will suffer or is likely to suffer if contraception is not given
- Prescribing contraception is in the young person's best interests

## 11. ABORTION

Children and young people may request abortion under the terms of the Abortion Act 1967 as amended in 1990. This provides that abortion may be carried out in pregnancies that do not exceed 24 weeks if:

- The continuation of the pregnancy would result in injury to the physical or mental health of the woman or any existing children in her family
- The termination is necessary to prevent that risk
- The continuation of the pregnancy would involve risk to the life of the mother, greater than if it were terminated
- There is a substantial risk that, if the child were born, it would suffer from such physical or mental

abnormalities as to be seriously handicapped

Under the Act the young person needs to be assessed by two doctors who must be satisfied that the abortion is justified.

The ethical justifications for abortion in young women are essentially similar to those in adults but a more paternalistic approach with appeal to best interests is reasonable in those who cannot consent because they lack the capacity to do so.

## 12. RESEARCH IN CHILDREN

There are sound ethical reasons to conduct ethical research in children, including:

- Children have unique, physiological, psychosocial status and specific needs
- Children have a right to receive treatments that are tested and evidence based
- Children are not mini-adults or animals so results from adult and animal research (though ethically preferable) may not be transferable to them
- Non-therapeutic research is ethically important in children
- Although children are vulnerable, this is not sufficient reason to exclude them from research from which they could benefit

Criteria for worthwhile 'general' research in children include:

- Identifiable prospect of benefit to children with minimal risk
- Well designed, well conducted
- Subject to informed consent freely given with opportunity to withdraw
- Primary motivation for conduct of research should not be financial or 'career'
- Sufficient statistical power
- Intention to report
- Appropriate ethical review

Research ethics committees have the responsibility for assessing whether research proposals are ethical. They are particularly concerned with assessment of risk, which is the likelihood of harm and the harm that may occur. Risk is often categorized according to level, namely:

- Minimal, e.g. questioning, observation, urine samples, use of spare clinical blood samples
- Low, e.g. venepuncture, injections
- High, e.g. biopsy, cardiac catheterization

In addition research ethics committees need to satisfy themselves that there are proper arrangements for obtaining informed consent, that they are particularly concerned with the information that is presented to children and parents, and that those obtaining consent are themselves competent to do so.

## 13. ETHICS AND LAW

There may be tensions between ethical and legal obligations, e.g. in relation to end-of-life issues. It is important that, whatever ethical views are held, practice conforms to the law.



---

# Child Law

---

## 14. AN INTRODUCTION

It is not feasible, here, to state comprehensively the law pertaining to paediatric medicine, let alone the body of law applicable to children. This section simply touches on some of the legal topics that frequently vex doctors, and reviews child law in England and Wales. The stage is set by consideration of the very wide remit of the Children Act 1989. Subsequently, the status of the child and those with parental responsibility are considered, before discussing the most frequently exercised issue of medical law in childhood, namely the provision of valid consent.

## 15. CHILDREN ACT 1989

The underlying themes of this Act are that:

- The child's welfare is paramount
- The courts should impose orders on children only if:
  - The imposition of an order would be better for the child than making no order at all
  - Any delays in decisions concerning the upbringing of a child are likely to prejudice the welfare of the child

The Act provides for state intervention in family matters, such as adjudication in issues of contact, residence, and in things that must and may not be done in relation to the child (i.e. Section 8 orders 'Contact, residence, Specific issue and Prohibited steps'). The Act ensures that local authorities provide services and support to families, and to 'children who are looked after by a local authority'. Finally, provision is made for the protection, care and supervision of children, establishing a 'threshold of harm' (Section 31(9): "harm' means ill-treatment or the impairment of health or development including for example, impairment suffered from seeing or hearing the ill-treatment of another').

## 16. WHAT IS A CHILD?

### 16.1 'Full legal capacity'

Childhood ends on the 18th birthday. At this point, transition to ‘Majority’ occurs and the new adult assumes all decision-making powers (although applicants for adoption and holders of Public offices cannot generally be under 21 years), including the ability to make their own decisions concerning health care. The significance of the 21st birthday as a landmark occasion in our society derives in part from this being the age of majority, until legislation in 1969 (the Family Law Reform Act 1969). Under the same Act, 16 and 17 year olds were given the legal right to agree to treatment independently of their parents, although the courts have not interpreted this statute as giving a right to refuse.

## 17. STATUS IN COURTS

Children traditionally have ‘no voice’ in courts (the word ‘infant’ derives from the Latin *infari*; no speech). This means that, in civil litigation, the child’s interests can be represented only through a litigation friend or a guardian *ad litem*; it is a parent’s right and duty to perform these roles, and it can be seen how conflicts of interest may arise between adult and child in these circumstances.

This rule also applies in family proceedings, where ‘children’s guardians’ now ensure that the feelings and wishes of the child are represented. However, it has been modified by the Children Act 1989, permitting a child with sufficient understanding to have an independent voice under some circumstances.

## 18. WHO ‘OWNS’ THE CHILD?

### 18.1 Children Act 1989

Although it is clear that no-one owns a child, the title serves as a reminder that until 1989, the legal emphasis was on parental rights and influence. This legacy derived from times when the father had exclusive and total power over his child, while a mother was merely entitled ‘only to reverence and respect’. Such power enabled unscrupulous fathers to earn money from the work of their children. Stealing children and effectively enslaving them reflected their economic value, and was legal until 1814. Progressive legislation addressed this appalling situation, but the central theme, of parental rights having overarching significance, was only finally reversed by the Act in 1989.

### 18.2 Parental responsibility

A key feature of the Act was to codify ‘parental responsibility’ as the central role of the adult who cares for the child. In most cases, it will obviously be the parents who have parental responsibility, but others may also share it, such as the local authority.

Defined as ‘all the rights, duties, powers, responsibilities and authority, which by law a parent of a

child has in relation to a child and his property', parental responsibility is automatically vested in the child's biological mother (although it should be noted that any of these basic rules would be invalidated by an adoption order). She, it is accepted in English law, is the person who gives birth to the child (as opposed to the genetic mother, in the case of some surrogates).

There is a legal presumption that the man who is married to the mother is the biological and thus legal father, whatever the truth of the situation. If married to the mother at the time of the birth, the father will have parental responsibility. An unmarried father whose name appears on the birth certificate on or after 1 December 2003 automatically has parental responsibility by marriage to the mother or it can be acquired by other unmarried fathers by formal agreements with the mother, or the court.

Guardians, local authorities, adoption agencies and prospective adopters can share parental responsibility with the parents but the parents only surrender their parental responsibility when the child reaches majority, or is adopted away from them. Under a court order, the local authority has the power to determine the extent to which a child's parent may meet his or her parental responsibility for the child.

In terms of the residual 'rights' of parenthood, the naming of the child, the determination of education and religion, and the right to appoint a guardian remain. The other 'incidents' of parenthood (i.e. to provide a home, to protect and maintain, to provide for education, to discipline, etc.) would largely be viewed as duties or responsibilities, placed by the state on the parent.

### 18.3 Wardship

In ancient times, wardship described a right to have custody over an infant who was the heir to land. Combined with the sovereign's powers to act as the parent of any abandoned (or orphaned) child, it can be seen that this was a potent mechanism for a land-hungry monarch (*parens patriae*: Latin: 'parent of the fatherland' or 'parent of the homeland'; in law, it refers to the power of the state to act as the parent of any child or the power to act on behalf of any individual who is in need of protection, such as an incapacitated individual or a child whose parents are unable or unwilling to take care of the child).

In the modern era, the High Court can use wardship as one means of exercising its *parens patriae* powers, to ensure that no important or major steps in the life of a ward of court can be taken without prior consent from the court. This certainly extends to medical treatments because for a ward of court, the court has parental responsibility. In general terms, one of the aims of the Children Act 1989 was to reduce the necessity for wardship proceedings, by incorporating its more worthwhile powers into the statute.

### 18.4 Guardians

Guardianship is confusing (see Bainham 2005), because there are several separate roles that adults play in relation to children which have acquired this label.

## Natural or parental guardian

Over centuries, the legitimate father has been the **natural or parental guardian** of the child, not least because of the property rights this conferred. English literature is peppered with references to fathers exercising their rights of guardianship, rarely to the children's advantage. A father could exercise all parental rights, to the exclusion of the mother, until 1973, when mothers were given equal rights and authority. Fathers retained some residual rights of this **natural guardianship** even after 1973. This was reflected in their ability to prohibit the mother's unilateral wish for a change of a child's surname following divorce, even if they had lost custody of the child. This **natural or parental guardianship** has been abolished by the Children Act 1989, removing the final vestiges of parental legal inequality.

## Guardians taking legal responsibility for a child after parental death

These **guardians** provide a vital, if under-utilized, function. They can be appointed (commonly) by parents or (less commonly) by courts. When parents contemplate the sad reality that they may die together, in an accident, leaving children, they may well wish to have influence over who brings up their orphaned family. Appointing a guardian enables them to exercise this influence, because the guardian will assume parental responsibility on the death of the second parent. Guardians may be appointed with no more formality than a signed and dated letter, and this rather surprising theme of informality applies to several aspects of guardianship. Nevertheless, it permits parents to avoid the nightmare of having their children brought up by their least-favourite relative in the event of their untimely and simultaneous death.

The family court may have to intervene if the second parent has died without appointing guardians, particularly if there is a dispute within the family as to who should look after the children. Have you got appropriate arrangements in place?

## Children's guardian

**Children's guardians** represent children in court during proceedings involving state intervention in the family; they are one of a number of individuals, collectively described as 'officers of the service', falling within the remit of the Children and Family Court Advisory and Support Service (CAFCASS). They are appointed on the basis of their expertise in social work and childcare law. Their role is to inform the court of the child's wishes and feelings, while providing all the information that may be relevant to the child's welfare. They are loosely equivalent to **guardians *ad litem***, who represent children in civil litigation.

## Special guardian

This is a new legal concept (introduced by the Adoption and Children Act 2002), providing legal security for permanent carers of children but falling short of adoption, for situations where adoption has been thought inappropriate for the child.

## 19. CONSENT

Those with parental responsibility have a duty to provide consent for the child's medical treatment.

Consent is required before any intervention, because society opposes the uninvited touch.

At its simplest, the outstretched hand, by implication, invites touching. However, the patient who consults their doctor does not assume that their very presence in the consulting room gives the doctor licence to touch them. The uninvited touch is, historically, an act of common assault. However, it is not the avoidance of this rather dramatic accusation that drives most contemporary doctors to obtain consent, although very occasionally the charge is still made.

What is far more relevant is the concept of negligence, where the doctor causes some harm by failing to deliver a reasonable standard of care to the patient, to whom there is undoubtedly a duty to provide such care.

One aspect of this standard of care is obtaining valid consent. This entails the provision of all necessary information for the patient to make an informed decision. Often, the only record of this provision is the annotated and signed consent form. This document thus acts both as a shield against a claim of assault, and objective evidence that some formal provision of information has occurred.

There are two excellent documents concerning consent which provide comprehensive guidelines (the *DH Reference Guide* and the BMA report of the Consent working party). The main questions to be considered when obtaining consent may be summarized as follows.

### **When is consent required?**

- Consent is required for any intervention

### **Who should obtain consent?**

- The person who will perform the proposed treatment

### **In what form should consent be taken?**

- There is no legal requirement for written consent, which can equally be verbal, or by acquiescence, provided the patient is correctly informed. However, a written document, which is signed by the patient, forms a piece of objective evidence that consent has been taken. Furthermore, if the document also records the details of the information given, it increases the certainty that relevant issues have been discussed. If the consent were verbal, it would be prudent to record the circumstances, topics discussed and outcome in the clinical notes

### **From whom should consent be obtained?**

- Anyone with parental responsibility for a child may provide consent for his or her medical treatment. To consent to treatment, an individual must have the capacity (i.e. intelligence and understanding) fully to understand what treatment is being proposed (see below)
- It is assumed that a young person of 16 years has such capacity, and because the law provides that they can give valid consent, no additional consent from parents is required. In the period between 16 and 18 years, if the young person is incapacitated, their parents may consent on their behalf

- A child of less than 16 years may give consent if capacity can be established, but the test is relatively rigorous

**In the absence of a parent, where a child is unable to consent because of lack of capacity, can the doctor treat in the emergency situation?**

- If emergency treatment is necessary to save life or avoid a significant deterioration in health, the doctor may treat on the basis of this necessity. However, the views of the parents and the child (if known), the likelihood of improvement with treatment and the need to avoid restricting future treatment options where possible must all be considered in this situation

**What information should be provided to obtain informed consent?**

- Any information that a reasonable patient would require when considering whether to consent to the proposed intervention should be discussed. This should include the certainties of diagnosis, the options for treatment (including non-treatment), a balanced opinion of the likely outcome of these options, and the purpose, risks, benefits and side effects of the intervention. The General Medical Council would also recommend ensuring that the name of the senior clinician is reiterated, together with a reminder that withdrawal from the treatment continues to be an option

## 20. CHILDREN'S CAPACITY

### 20.1 16–17 years

There is a legal presumption that these young people have the capacity to consent, so there is no requirement for clinicians to test capacity in this age group. However, if there is doubt that an individual is competent to provide consent, their competence should be assessed according to the criteria used for any adult (according to *Re C (Adult: Refusal of Medical Treatment)* [1994] 1 All ER 819), and reiterated by the Mental Capacity Act 2005 s3(1). According to Grubb (2004) the patient must be able to:

- Comprehend and retain the relevant information
- Believe it
- Weigh it in the balance so as to arrive at a choice

Refusal of therapy, particularly if the treatment is for life-threatening disease, gives more difficulty, and legal advice should be sought. Despite wishing to uphold the autonomy of competent children, English courts effectively prohibit children from refusing treatment that will save them from death or serious permanent harm.

### 20.2 Preschool

It is self-evident that children in this age group are unable to provide valid consent but they still have autonomy and their interests should be considered. It is good practice to involve them where possible in the process of obtaining consent, particularly offering to answer their questions, and to remind them of the obvious consequences of a procedure (e.g. the scar).

## 20.3 The intervening years: Gillick competence

The child who has yet to reach 16 years is presumed, by the law, to be incapable of providing consent. However, some children who quite clearly possess a degree of capacity may be able to demonstrate their competence. If they can, they may provide consent independently of their parents. However, it is both good manners and good practice to involve their parents; and it will be rare for such parental involvement to be inappropriate, unless confidentiality is an issue. In determining whether a child might have capacity for consenting to a particular procedure, their age is probably the least important consideration. The House of Lords have provided the means for the determination, in their ruling on the Gillick case (*Gillick v West Norfolk & Wisbech AHA* [1985] 3 All ER 402, HL). The child would need to:

- Understand that a choice exists
- Understand the purpose and nature of the proposed treatment
- Understand the risks, benefits and alternatives
- Understand the consequences of not undergoing the treatment

Furthermore, the child must:

- Be able to remember the information for long enough to make a considered decision
- Be free from undue pressure

It is clear that the ability of the child to pass this ‘test’ is entirely dependent on both the proposed procedure and the child’s experience. It is not difficult to picture 14 year olds with newly diagnosed leukaemia, bewildered and terrified, who would be entirely incapable of providing valid consent to a diagnostic lumbar puncture. On the other hand, a younger child who has spent months on the oncology ward, has already had numerous similar procedures, and witnessed the consequences in many of his fellow patients, may well be competent.

It should be reiterated that the Gillick test, understandably, sets a high threshold for capacity that would probably be unattainable by many adults.

As with the 16 to 17 year olds, the ability of Gillick-competent children to provide valid consent does not extend to a right to refuse.

## 20.4 Fraser guidelines

Emerging from the House of Lords judgement, Lord Fraser also gave guidance on how the Gillick principle could be applied to the provision of contraceptives to young people. These guidelines emphasize the importance of parental support, acknowledging confidentiality and weighing the best interests of the child (see BMA 2004). They also take account of the risk that the patient may have unprotected sex if the contraception is denied, and the potential effects on their mental and physical



health.

## 21. FURTHER READING

Bainham A (2005). *Children: The modern law*. London: Jordan Publishing.

British Medical Association (2001). *Report of the Consent Working Party*. London: BMA Medical Ethics Department.

British Medical Association (2004). *Medical Ethics Today*. London: BMA Medical Ethics Department.

British Medical Association (2007). *Withholding and Withdrawing Life-prolonging Medical Treatment: Guidance for decision-making*, 3rd edn. London: BMA Publications.

Department of Health (2001). *Reference Guide to Consent for Examination or Treatment*. London: DH. Available at: [www.doh.gov.uk/consent](http://www.doh.gov.uk/consent).

Diekema DS, Botkin JR (2009). Clinical report – forgoing medically provided nutrition and hydration in children. *Pediatrics* **124**:813–22.

General Medical Council (2010). *Treatment and Care towards the End of Life*. London: GMC.

Grubb A (2004). *Principles of Medical Law*. Oxford: Oxford University Press.

Hope T, Savulescu J, Hendrick J (2003). *Medical Ethics and Law: The Core Curriculum*. London: Churchill Livingstone.

Kennedy I, Grubb A (2000). *Medical Law Text and Materials*, 3rd edn. London: Butterworths.

Montgomery J (2002). *Health Care Law*, 2nd edn. Oxford: Oxford University Press.

Nuffield Council on Bioethics (2009). *Critical Care Decisions in Fetal and Neonatal Medicine: Ethical issues*. London: Nuffield Council on Bioethics.

Raphael DD (1994). *Moral Philosophy*, 2nd edn. Oxford: Oxford University Press.

Royal College of Paediatrics and Child Health (2004). *Withholding or Withdrawing Life Sustaining Treatment in Children: A framework for practice*, 2nd edn. London: RCPCH. Available at: [www.rcpch.ac.uk](http://www.rcpch.ac.uk).

Royal College of Paediatrics and Child Health: Ethics Advisory Committee (2000). Guidelines for the ethical conduct of medical research involving children. *Arch Dis Child* **82**:177–82.



Sokol DK, Bergson G (2000). *Medical Ethics and Law; Surviving the wards and passing exams*. London: Trauma Publishing.

Wheeler RA (2006). Gillick or Fraser? A plea for consistency over competence in children. *BMJ* **332**;807.

Wheeler RA (2010). Presumed or implied; It's not consent. *Clin Risk* **16**;1–2.

## **Website**

UK Clinical Ethics Network: [www.ethics-network.org.uk](http://www.ethics-network.org.uk)

---

# Chapter 10

## Gastroenterology and Nutrition

*Mark Beattie and Hemant Bhavsar*

---

### CONTENTS

#### **1. Basic anatomy and physiology**

- [1.1 Anatomy](#)
- [1.2 Digestion](#)

#### **2. Nutrition**

- [2.1 Nutritional requirements](#)
- [2.2 Nutritional assessment](#)
- [2.3 Breast-feeding](#)
- [2.4 Iron](#)
- [2.5 Folate](#)
- [2.6 Vitamin B<sub>12</sub>](#)
- [2.7 Zinc](#)
- [2.8 Fat-soluble vitamins](#)
- [2.9 Nutritional impairment](#)
- [2.10 Protein–energy malnutrition](#)
- [2.11 Faltering growth](#)
- [2.12 Organic causes of faltering growth](#)
- [2.13 Malabsorption](#)

#### **3. Nutritional management**

- [3.1 Nutritional supplementation](#)
- [3.2 Enteral nutrition](#)
- [3.3 Parenteral nutrition](#)
- [3.4 Re-feeding syndrome](#)
- [3.5 Intestinal failure](#)
- [3.6 Home parenteral nutrition](#)

## **4. Food allergy and intolerance**

- [4.1 Cows' milk protein intolerance](#)
- [4.2 Peanut allergy](#)
- [4.3 Food-induced anaphylaxis](#)
- [4.4 Carbohydrate intolerance](#)

## **5. Gastro-oesophageal reflux**

- [5.1 Differential diagnosis of reflux oesophagitis](#)
- [5.2 Feeding problems in neurodisability](#)
- [5.3 Eosinophilic oesophagitis](#)
- [5.4 Achalasia](#)
- [5.5 Dysphagia](#)

## **6. Peptic ulcer disease**

- [6.1 \*Helicobacter pylori\* infection](#)
- [6.2 Other causes of antral gastritis and peptic ulceration](#)
- [6.3 Zollinger–Ellison syndrome](#)

## **7. Chronic diarrhoea**

- [7.1 Congenital diarrhoea/intractable diarrhoea of infancy](#)
- [7.2 Post-enteritis syndrome](#)
- [7.3 Cows' milk protein sensitive enteropathy](#)
- [7.4 Giardiasis](#)
- [7.5 Exocrine pancreatic insufficiency](#)
- [7.6 Bacterial overgrowth \(small bowel\)](#)
- [7.7 Intestinal lymphangiectasia](#)
- [7.8 Protein-losing enteropathy](#)
- [7.9 Chronic non-specific diarrhoea](#)

## **8. Coeliac disease**

## **9. Abdominal pain**

- [9.1 Recurrent abdominal pain](#)
- [9.2 Functional gastrointestinal disorders](#)

## **10. Inflammatory bowel disease**

- [10.1 Crohn disease](#)
- [10.2 Ulcerative colitis](#)
- [10.3 Differential diagnosis of colitis](#)
- [10.4 Eosinophilic enterocolitis](#)
- [10.5 Pseudomembranous colitis](#)

## **11. Gastrointestinal bleeding**

- [11.1 Common causes of gastrointestinal bleeding](#)

[11.2 Intussusception](#)

[11.3 Meckel diverticulum](#)

[11.4 Polyposis](#)

## **12. Gastroenteritis**

## **13. Constipation**

[13.1 Perianal streptococcal infection](#)

[13.2 Hirschsprung disease](#)

## **14. Further reading**

---

# Gastroenterology and Nutrition

---

## 1. BASIC ANATOMY AND PHYSIOLOGY

### 1.1 Anatomy

#### **Oesophagus**

Outer longitudinal and inner circular muscle layers with myenteric plexus in between. Mucosa is lined by stratified squamous epithelium. Adult length 25 cm.

#### **Stomach**

Lined by columnar epithelium. Chief cells produce pepsin. Parietal cells produce gastric acid and intrinsic factor. Secretions in adults are 3 l/day. Gastric acid secretion is stimulated by vagal stimulation, gastrin and histamine via  $H_2$ -receptors on parietal cells. Secretion is inhibited by sympathetic stimulation, nausea, gastric acidity and small intestinal peptides. Blood supply from coeliac axis.

#### **Small intestine**

Main function is absorption, mostly in the duodenum and jejunum, apart from bile salts and vitamin  $B_{12}$  which are absorbed in the terminal ileum. Blood supply from mid-duodenum onwards is the superior mesenteric artery. Adult length 2–3 metres.

#### **Colon**

Functions primarily for salt and water reabsorption. Blood supply from superior mesenteric artery until the distal transverse colon and then the inferior mesenteric artery after that. Approximately 1 m long in adults.

#### **Pancreas**

Retroperitoneal. Endocrine function (2% of tissue mass) and exocrine function (98%). Blood supply

from coeliac axis.

Congenital anomalies of the gastrointestinal system are described separately in Chapter 17.

## 1.2 Digestion

### Carbohydrate digestion

- Carbohydrates are consumed as monosaccharides (glucose, fructose, galactose), disaccharides (lactose, sucrose, maltose, isomaltose) and polysaccharides (starch, dextrins, glycogen)
- Salivary and pancreatic amylase break down starch into oligosaccharides and disaccharides. Pancreatic amylase aids carbohydrate digestion but carbohydrate digestion is not dependent upon it
- Disaccharidases (maltase, sucrase, lactase) in the microvilli hydrolyse oligo- and disaccharides into monosaccharides:
  - Maltose into glucose
  - somaltose into glucose
  - Sucrose into glucose and fructose
  - Lactose into glucose and galactose
- Monosaccharides are then absorbed, glucose and galactose by an active transport mechanism and fructose by facilitated diffusion

### Protein digestion

- In the stomach, gastric acid denatures protein and facilitates the conversion of pepsinogen into pepsin
- Trypsin, chymotrypsin and elastase, secreted as the inactive precursors, are produced by the exocrine pancreas. Enterokinase (secreted in the proximal duodenum) activates trypsin and trypsin further activates trypsin, chymotrypsin and elastase
- These proteases convert proteins into oligopeptides and amino acids in the duodenum
- The small intestine absorbs free amino acids and peptides by active transport and these substances then enter the portal vein and are carried to the liver.

### Fat digestion

- Entry of fats into the duodenum causes release of pancreozymin–cholecystokinin which stimulates the gallbladder to contract
- Hydrolysis of triglycerides by pancreatic lipase takes place
- Free fatty acids, glycerol and monoglycerides are emulsified by bile salts to form micelles which are then absorbed along the brush border of mucosal cells
- Short-chain fatty acids enter the portal circulation bound to albumin. Long-chain fats are re-esterified within the mucosal cells into triglycerides which combine with lesser amounts of protein, phospholipid and cholesterol to create chylomicrons
- Chylomicrons enter the lymphatic system and are transported via the thoracic duct into the

bloodstream

## Pancreatic function

The pancreas secretes more than a litre of pancreatic juice per day, which is bicarbonate rich and contains enzymes for the absorption of carbohydrate, fat and protein. Faecal elastase is a commonly used screen of pancreatic function.

## Gut hormones

The main gut hormones are:

- **Gastrin** – stimulated by vagal stimulation, distension of the stomach. Stimulates gastric acid, pepsin and intrinsic factor. Stimulates gastric emptying and pancreatic secretion
- **Secretin** – stimulated by intraluminal acid. Stimulates pancreatic bicarbonate secretion, inhibits gastric acid and pepsin secretion, and delays gastric emptying
- **Cholecystokinin–pancreozymin** – stimulated by intraluminal food. Stimulates pancreatic bicarbonate and enzyme secretion. Stimulates gallbladder contraction, inhibits gastric emptying and gut motility

Other gut hormones include:

- **Gastric inhibitory peptide** – stimulated by glucose, fats and amino acids; inhibits gastric acid secretion, stimulates insulin secretion and reduces motility
- **Motilin** – stimulated by acid in the small bowel; increases motility
- **Pancreatic polypeptide** – stimulated by a protein-rich meal; inhibits gastric and pancreatic secretion
- **Vasoactive intestinal peptide (VIP)** – neural stimulation; inhibits gastric acid and pepsin secretion; stimulates insulin secretion; reduces motility

## Enterohepatic circulation

Bile is produced by the liver and stored in the gallbladder. It is secreted into the duodenum after gallbladder contraction (stimulated by cholecystokinin–pancreozymin release). Bile acids aid fat digestion and are formed from cholesterol. Primary bile acids are produced in the liver, and secondary bile acids are formed from primary bile acids through conjugation with amino acids by the action of intestinal bacteria. Primary and secondary bile acids are deconjugated in the intestine, reabsorbed in the terminal ileum and transported back to the liver bound to albumin for recirculation.

## 2. NUTRITION

### 2.1 Nutritional requirements

This is age dependent and there are standard tables available (reference nutrient intake, RNI). The energy needs per kilogram of the infant are higher than the older child.

## Daily requirements

### Infant 0–3 months

• Fluid	150 ml/kg
• Calories	100 kcal/kg
• Protein	2.1 g/kg
• Sodium	2-3 mmol/kg
• Potassium	1.5–3.0 mmol/kg

### 12-year-old boy

• Fluid	55 ml/kg
• Calories	50 kcal/kg
• Protein	1 g/kg
• Sodium	2 mmol/kg
• Potassium	2 mmol/kg

Energy requirements list calories but nutrient and micronutrient requirements are also important to ensure that intake is balanced. It is essential, for example, to have an appropriate balance of fat, carbohydrate and protein. Calcium is essential for bone growth. Iron is required to prevent anaemia.

Energy requirements include resting energy expenditure (basal metabolic rate, BMR), which represents 60–70% of requirements and the component that arises as a consequence of physical activity (physical activity level).

Physical status (metabolic condition, bedridden, physical activity level) will impact on requirements.

## 2.2 Nutritional assessment

- It is important to take a careful history, assess intake, consider requirements and perform basic anthropometry including weight, height (length in children who are unable to stand) and head circumference
- Body mass index (BMI) is a useful marker of ‘fatness’ measured as  $(\text{weight})/(\text{height}^2)$  in  $\text{kg}/\text{m}^2$ . The values need to be plotted against age on standard charts
- Other methods of assessing nutritional state include skin-fold thickness as an estimate of fat mass and mid-arm circumference as an estimate of lean body mass. Standard age-matched reference values are available



- Bioimpedance and indirect calorimetry as research tools are also used

## **Important factors in the history**

Consider the following:

- Conditions that interfere with intake
- Conditions that interfere with absorption, e.g. intestinal resection
- Conditions associated with increased losses, e.g. diarrhoea, vomiting
- Condition associated with increased needs, e.g. fever, sepsis, tissue injury
- Conditions that restrict intake, e.g. cardiac disease, renal disease, food intolerance
- Gastrointestinal conditions, e.g. gastro-oesophageal reflux, constipation

Ensure that you understand relevant social and family factors that may impact on the child's nutrition.

## **2.3 Breast-feeding**

### **Breast-feeding and infection**

Ten per cent of the protein in mature breast milk is secretory immunoglobulin A (IgA). Lymphocytes, macrophages, proteins with non-specific antibacterial activity and complement are also present. There have been many studies in developing countries to show that infants fed formula milk have a higher mortality and morbidity particularly from gastrointestinal infection. In the UK, studies have shown:

- Breast-feeding for more than 13 weeks reduces the incidence of gastrointestinal and respiratory infections
- The response to immunization with the Hib (*Haemophilus influenzae* type b) vaccine is higher in breast-fed than in formula-fed infants
- The risk of necrotizing enterocolitis in low-birthweight babies is lower in those who are breast-fed

### **Breast-feeding and allergy**

The incidence of atopic eczema in infants born to atopic mothers is reduced by breast-feeding. Overall, however, there is no definitive proven reduction in atopy apart from this specific circumstance.

### **Breast-feeding and neurological development**

Although there are confounding variables that make study of this subject difficult, there is work that suggests that neurological development is enhanced in breast-fed infants.

### **Breast-feeding and diabetes**

Infants who are breast-fed have a reduced risk of developing diabetes.

## **Breast-feeding and infantile colic**

There is no good evidence to show that breast-feeding reduces the incidence of infantile colic.

## **Contraindications to breast-feeding**

Maternal drugs and breast-feeding are discussed in Chapter 5, Section 6.2 and Chapter 17.

- With regard to tuberculosis, infants can be immunized at birth with isoniazid-resistant BCG and treated with a course of isoniazid
- With regard to human immunodeficiency virus (HIV), the virus has been cultured from breast milk and is transmitted in it. In the western world this means that breast-feeding is contraindicated in HIV-positive mothers, because it will increase the perinatal transmission rate. The problem is not so straightforward in the developing world where the risks of bottle-feeding are high because of contaminated water supplies

## **Term and preterm formula**

The principal differences are that preterm formula contains more electrolytes, calories and minerals. All of the following are higher in preterm than in term formula: energy, protein, carbohydrate, fat, osmolality, sodium, potassium, calcium, magnesium, phosphate and iron.

## **Human (breast) milk and cows' milk**

The energy content is the same. Human milk contains less protein than cows' milk; cows' milk having a much higher casein content. The fat, although different qualitatively, is the same in amount. Human milk contains more carbohydrate. Cows' milk contains more of all the minerals except iron and copper.

## **2.4 Iron**

- Dietary sources include cereals, red meat (particularly liver), fresh fruit and green vegetables
- Absorbed from the proximal small bowel; vitamin C, gastric acid and protein improve absorption; 5–10% of dietary iron is absorbed
- Deficiency causes hypochromic microcytic anaemia. Associated with poor appetite and reduced intellectual function
- Common causes of deficiency include poor diet (particularly prolonged or excess milk feeding), chronic blood loss, malabsorption
- Low serum iron/high transferrin suggests deficiency; low iron/low transferrin suggests chronic disease. Ferritin is an indicator of total body stores but is also an acute-phase reactant
- Treatment is directed against the underlying cause. Dietary advice and iron supplements, of which numerous commercial preparations are available, are indicated in most patients. Side effects of

iron supplements include abdominal discomfort and constipation. Iron supplements can be fatal in overdose

## 2.5 Folate

- Dietary sources include liver, green vegetables, cereals, orange, milk, yeast and mushrooms.  
Excessive cooking destroys folate
- Absorbed from the proximal small bowel
- Deficiency causes megaloblastic anaemia, irritability, poor weight gain and chronic diarrhoea.  
Thrombocytopenia can occur
- The serum folate reflects recent changes in folate status and the red-cell folate is an indicator of the total body stores
- Treatment of deficiency is with oral folic acid
- Folate levels are not affected by the acute-phase response
- Folate deficiency in mother around the time of conception causes neural tube defects in the baby

### Causes of folate deficiency

- Reduced intake
- Malabsorption, e.g. coeliac disease
- Congenital folate malabsorption (autosomal recessive)
- Increased requirements (infancy, pregnancy, exfoliative skin disease)
- Drugs, e.g. methotrexate, trimethoprim, anticonvulsants, oral contraceptive pill

## 2.6 Vitamin B<sub>12</sub>

- Dietary sources include foods of animal origin, particularly meat
- Absorbed from the terminal ileum, facilitated by gastric intrinsic factor
- Deficiency causes megaloblastic anaemia, low vitamin B<sub>12</sub> and increased methylmalonic acid in the urine
- Clinical features include anaemia, glossitis, peripheral neuropathy, subacute combined degeneration of the cord and optic atrophy
- Causes include pernicious anaemia (rare in childhood); gastric- and parietal-cell antibodies are usually positive
- Other causes of vitamin B<sub>12</sub> deficiency include poor intake (vegan diet) and malabsorption, e.g. blind-loop, post-resection
- Treatment is with vitamin B<sub>12</sub>, usually given intramuscularly once or twice a week initially then 3-monthly. Folic acid is also needed

## 2.7 Zinc

- Dietary sources include beef, liver, eggs and nuts
- Deficiency occurs secondary to poor absorption rather than poor intake
- Clinical features include anaemia, growth retardation, periorofacial dermatitis, immune deficiency, diarrhoea
- Responds well to oral zinc

## **Acrodermatitis enteropathica**

- Autosomal recessive inheritance
- Basic defect is impaired absorption of zinc in the gut
- Presents with skin rash around the mouth and perianal area, chronic diarrhoea at the time of weaning and recurrent infections. The hair has a reddish tint; alopecia is characteristic. Superinfection with *Candida* sp. is common as are paronychia, dystrophic nails, poor wound healing and ocular changes (photophobia, blepharitis, corneal dystrophy)
- Diagnosis is by serum zinc levels and the constellation of clinical signs. Measurement is difficult because the serum zinc is low as part of the acute-phase response. Measurement of white-cell zinc levels is more accurate. The plasma metallothionein level can also be measured. Metallothionein is a zinc-binding protein that is decreased in zinc deficiency but not in the acute-phase response
- Zinc deficiency in the newborn can produce a similar clinical picture
- The condition responds very well to treatment with oral zinc

## **2.8 Fat-soluble vitamins**

### **Vitamin A**

- Deficiency causes night blindness, poor growth, xerophthalmia, follicular hyperplasia and impaired resistance to infection
- Excess causes carotenaemia, hyperostosis with bone pain, hepatomegaly, alopecia and desquamation of the palms. Acute intoxication causes raised intracranial pressure
- Dietary sources are milk, fat, fruit and vegetables, eggs and liver
- Vitamin A has an important role in resistance to infection particularly at mucosal surfaces. In developing countries where vitamin A deficiency is endemic, vitamin A reduces the morbidity and mortality associated with severe measles

### **Vitamin E**

- Is an antioxidant
- Found in green vegetables and vegetable oils
- Deficiency causes ataxia, peripheral neuropathy and retinitis pigmentosa

### **Abetalipoproteinaemia**

- Autosomal recessive inheritance
- Pathogenesis is failure of chylomicron formation with impaired absorption of long-chain fats with fat retention in the enterocyte
- Presents in early infancy with faltering growth, abdominal distension and foul-smelling, bulky stools
- Symptoms of vitamin E deficiency (ataxia, peripheral neuropathy and retinitis pigmentosa) develop later
- Diagnosis is by low serum cholesterol, very low plasma triglyceride level, acanthocytes on examination of the peripheral blood film and absence of betalipoprotein in the plasma
- Treatment is by substituting medium-chain triglycerides for long-chain triglycerides in the diet (absorbed via the portal vein rather than the thoracic duct). In addition, high doses of the fat-soluble vitamins (A, D, E and K) are required. Most of the neurological abnormalities are reversible if high doses of vitamin E are given early

## **Vitamin D**

- Vitamin D is important for calcium homeostasis and optimal bone growth
- Sources are fish oil, vegetable oil, skin synthesis by ultraviolet B light and egg yolks
- Two main forms – vitamin D<sub>2</sub> and vitamin D<sub>3</sub>. Vitamin D<sub>3</sub>, also known as cholecalciferol, is either made in the skin or obtained in the diet from fatty fish. Vitamin D<sub>2</sub>, also known as ergocalciferol, is obtained from irradiated fungi, such as yeast. In order to become active, vitamin D requires two sequential hydroxylations to form 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, which happens in the liver and kidney respectively.
- Deficiency can occur because of dietary deficiency (e.g. prolonged breast-feeding, inadequate diet), inadequate exposure to sunlight, malabsorption, medications
- Vitamin D deficiency leads to decreased calcium absorption, low plasma calcium, high alkaline phosphatase and raised parathyroid hormone
- Deficiency results in rickets, impaired bone formation and growth. Older children can get bowing of long bones, enamel hypoplasia, kyphoscoliosis and pelvic deformity
- 25-Hydroxyvitamin D is the most accurate way to measure how much vitamin D is in the body
- Oral calciferol and cholecalciferol are used as treatment. The principal aim of therapy is to replenish vitamin D stores; patients are then continued on a lower maintenance dose. Large bolus doses are also equally effective
- Vitamin D deficiency is very common in the UK and under-diagnosed. From a public health perspective, primary prevention of vitamin D deficiency in the UK is socially as well as medically justifiable. The key groups for health-care professionals to target are infants, children, adolescents and pregnant women, particularly those with dark skin. Other high-risk groups are elderly and institutionalized people

## **Vitamin K**

- Found in cows' milk, green leafy vegetables and pork; very little in breast milk
- Deficiency in the newborn presents as haemorrhagic disease of the newborn. This usually presents on day 2 or 3 with bleeding from the umbilical stump, haematemesis and melaena, epistaxis or

excessive bleeding from puncture sites. Intracranial bleeding can occur. Diagnosis is by prolongation of the prothrombin and partial thromboplastin times, with the thrombin time and fibrinogen levels being normal. Treatment is with fresh frozen plasma and vitamin K

- There is no proven association between intramuscular vitamin K and childhood cancer

## 2.9 Nutritional impairment

### Energy balance

A positive energy balance implies that intake exceeds requirements and a negative energy balance implies that intake is less than requirements. It is important to remember that requirements during childhood include those needed for growth.

### Pathogenesis of malnutrition

It is essential to think about the pathogenesis of malnutrition when assessing nutrition and looking at nutritional supplementation. Malnutrition can only result from:

- Inadequate intake or excessive losses
- Increased metabolic demand without increased intake
- Malabsorption

One or all of these may contribute to malnutrition in an individual.

A good example is cystic fibrosis in which:

- Pancreatic malabsorption causes increased losses
- Increased energy needs are caused by:
  - Chronic cough
  - Dyspnoea
  - Recurrent infection
  - Inflammation
- Reduced intake is caused by:
  - Anorexia
  - Vomiting
  - Psychological problems

Together, all of these factors result in an energy deficit. They all need to be taken into account when nutritional supplementation is considered.

## 2.10 Protein–energy malnutrition

**Marasmus** is characterized by muscle wasting and depletion of the body fat stores. **Kwashiorkor** is characterized by generalized oedema with flaky or peeling skin and skin rashes. Most children with malnutrition – rare in the western world – exhibit a combination of the two. Micronutrient deficiencies are common in these children.

## 2.11 Faltering growth

Faltering growth (previously called ‘failure to thrive’) refers to not only failure of growth but also impairment of other aspects of a child’s wellbeing. It is common in infancy. It occurs because of one or a combination of the following:

- Failure of carer to offer adequate calories
- Failure of the child to take sufficient calories
- Failure of the child to retain adequate calories

Clearly this can be organic or non-organic. Insufficient calories may be offered as a consequence of parental neglect or because of a failure of the carer to appreciate the calorie requirements of the child. Insufficient calories may be taken as a consequence of feeding difficulties (e.g. cerebral palsy) or increased needs (e.g. cystic fibrosis), and calories may not be retained because of absorptive defects or loss through vomiting or diarrhoea.

It is important to consider other causes that can influence growth such as familial short stature, genetic abnormality, birth size (intrauterine growth retardation), psychological deprivation and environmental factors (poverty).

The investigation of faltering growth is generally fruitful only when specific pointers to organic problems are elucidated in the history or on physical examination.

The management of non-organic faltering growth requires health visitor input and often dietary assessment. In difficult cases hospital admission is indicated for multidisciplinary evaluation and to ensure an adequate weight gain can be obtained if sufficient calories are given.

## 2.12 Organic causes of faltering growth

This list provides examples only and is by no means exhaustive:

- Gastrointestinal – coeliac disease, cows’ milk-protein intolerance, gastro-oesophageal reflux
- Renal – urinary tract infection, renal tubular acidosis
- Cardiopulmonary – cardiac disease, cystic fibrosis, bronchopulmonary dysplasia
- Endocrine – hypothyroidism, growth hormone deficiency
- Neurological – cerebral palsy
- Infection/immunodeficiency – HIV, malignancy
- Metabolic – inborn errors of metabolism

- Congenital – chromosomal abnormalities
- ENT – adenotonsillar hypertrophy

## 2.13 Malabsorption

Malabsorption is difficulty absorbing nutrients from food. Several malabsorption syndromes have been described. They can be genetically determined or acquired, and affect one or more of the several mechanisms responsible for the absorption of food; they result in chronic diarrhoea, abdominal distension and failure to thrive:

- Genetically determined malabsorption syndromes – coeliac disease and cystic fibrosis are two very common causes
- Common acquired causes include cows' milk protein intolerance, acute enteritis, post-enteritis syndrome
- A detailed list of causes is described in Section 7 on chronic diarrhoea

## 3. NUTRITIONAL MANAGEMENT

### 3.1 Nutritional supplementation

Nutritional supplementation should be with the help of a dietician. It is essential, however, to have some background information and to:

- treat underlying pathology, which may be a factor
- assess the child's requirements
- give additional calories either by increasing the calorie density of feed or giving feed by a different route, e.g. nasogastric tube, gastrostomy tube or parenterally

**Enteral nutrition** refers to that given either directly (by mouth) or indirectly (via nasogastric tube or gastrostomy) into the gastrointestinal tract. **Parenteral nutrition** is given into either the peripheral or the central veins, usually the latter.

It may be helpful to consider specific scenarios:

*A 6-month-old infant with congenital heart disease is failing to thrive – comment on his nutritional status. What nutritional supplementation would you recommend?*

In this infant the poor nutritional state will be as a consequence of increased metabolic demands and poor intake secondary to breathlessness. Supplementation would be by increasing the calorie density of feeds and consideration of other methods of administration such as via a nasogastric tube. It is obviously also of importance to maximize medical therapy of the heart disease.



*This 6-month-old infant has bronchopulmonary dysplasia and severe faltering growth. Comment on possible causes.*

In this infant the above applies. In addition, other factors may be relevant such as chronic respiratory symptoms, gastro-oesophageal reflux and neurodevelopmental issues. Supplementation would be by increasing calorie density of feeds and considering using a nasogastric tube or gastrostomy to give the feed. In addition, investigation for problems such as gastro-oesophageal reflux may be considered.

*This 3-month-old infant, born at 29 weeks' gestation, had a massive resection for volvulus in the neonatal period and has poor feed tolerance, parenteral nutrition (PN) dependence and severe liver disease. What strategies are required in this child's subsequent management?*

This child has intestinal failure with persistent PN dependency and liver disease. The priority is to maximize enteral intake which will reduce the likelihood of progression of the liver disease. A hydrolysed feed given by continuous infusion will probably be tolerated best. PN should be weaned only when the feed is tolerated and absorbed. Loperamide may reduce transit. Bacterial overgrowth is likely and should be managed with cyclical antibiotics. Macro- and micronutrients should be checked to ensure that they are adequate. Attention should be given to promoting the child's oral feeding skills.

*This 13-year-old boy has cerebral palsy. Comment on his nutritional status. What strategies could be used to improve his nutrition? Why do you think his nutritional status is so poor?*

This child's principal problem is likely to be with intake, either because of reflux or secondary to bulbar problems, or both. In addition to nutritional supplements, this child may benefit from help with feeding practices including the involvement of a dietician, speech and language therapist, occupational therapist and neurodevelopmental paediatrician. Other medical problems may be relevant such as recurrent chest infections secondary to aspiration and intractable fits. Consideration needs to be given to feeding via nasogastric tube or gastrostomy tube if appropriate. In some instances a fundoplication will also be required.

*This boy has cystic fibrosis. Comment on his nutritional status. What can be done to help?*

The additional factor in this child is malabsorption for which pancreatic supplementation is required. Children with cystic fibrosis often dislike food and need either a nasogastric tube or gastrostomy to help with administration. The energy requirements are high and calorie supplementation with energy-dense supplements is required.

## **Nutritional supplements**

- Normal infant feeds or milk contain 0.7 kcal/ml
- Feeds can be concentrated
- Carbohydrate supplements can be used, usually as glucose polymer in powder form to add to feeds
- Combined carbohydrate and fat supplements can be used
- Feeds with a higher calorie density can be used, e.g. 1 kcal/ml, 1.5 kcal/ml

- Special feeds can be used, e.g. hydrolysed protein formula feeds, soya-based feeds, lactose-free feeds, medium-chain triglyceride-based feeds
- Milk-based or juice-based supplements can be given
- There are many commercially available products available

## 3.2 Enteral nutrition

Enteral feeding strictly refers to enteral feed given directly into the gastrointestinal tract. For the purpose of this section, an enteral feed has been considered as a supplementary feed, i.e. not including foods normally taken by mouth, and therefore refers principally to feeds given by nasogastric or nasojejunal tube, gastrostomy, gastrojejunostomy or jejunostomy.

### Indications for enteral tube feeding

- Insufficient energy intake by mouth
- Wasting
- Stunting

### Diseases for which enteral nutrition may be indicated

#### Gastrointestinal

- Short-bowel syndrome
- Inflammatory bowel disease
- Pseudo-obstruction
- Chronic liver disease
- Gastro-oesophageal reflux
- Glycogen storage disease types I and III
- Fatty acid oxidation defects

#### Neuromuscular disease

- Coma and severe facial and head injury
- Severe learning disability and cerebral palsy
- Dysphagia secondary to cranial nerve dysfunction, muscular dystrophy or myasthenia gravis

#### Malignant disease

- Obstructing disease
- Head and neck
- Oesophagus
- Stomach
- Abnormality of deglutition after surgical intervention

- Gastrointestinal side effects from chemotherapy and/or radiotherapy
- Terminal supportive care

## **Pulmonary disease**

- Bronchopulmonary dysplasia
- Cystic fibrosis
- Chronic lung disease

## **Congenital abnormalities**

- Tracheo-oesophageal fistula
- Oesophageal atresia
- Cleft palate
- Pierre Robin syndrome

## **Other**

- Anorexia nervosa
- Cardiac cachexia
- Chronic renal disease
- Severe burns
- Severe sepsis
- Severe trauma

## **Choice of feed type**

A wide range of feeds are available and the decision about which to use is based on the child's needs. Factors that are of relevance include whether the enteral feed will be the sole source of feeding, in which case the feed needs to be nutritionally complete, or whether the feed is going to be given as a supplement. Feed tolerance and calorie requirements are relevant. A modified feed may be required, e.g. lactose free in a child with carbohydrate intolerance. Factors such as fibre content and calorie density are also important, particularly if supplementary feeding is going to be long term.

A hydrolysed protein is one that is broken down into oligopeptides and peptides. A hydrolysed protein milk formula is therefore one that does not contain whole protein. An elemental formula is a hydrolysed protein formula in which the protein is broken down into amino acids.

Hydrolysed protein formula feeds are used in children with cows' milk allergy, enteropathies, e.g. post-gastroenteritis, post-necrotizing enterocolitis, short-gut syndrome, severe eczema and Crohn disease.

## **Choice of feed regimen**

This will depend on a combination of requirements, tolerance and factors such as gastric emptying. Options include bolus feeding and continuous feeding or a combination of the two.

In the severely malnourished child, the volume and calorie density of a new feed regimen may need to be increased slowly, as tolerated, over a few days. This avoids metabolic upset (re-feeding syndrome) in the vulnerable child, e.g. severe postoperative weight loss, anorexia nervosa.

## **Dysmotility**

The motility of the gut is a key factor in feed tolerance. Preterm infants, and children with cerebral palsy, may have delayed gastric emptying which can impact significantly on the ability to feed, particularly if nutrition is dependent on nasogastric or gastrostomy feeding. Abdominal pain, bloating and constipation are common features of gut dysmotility.

It may be necessary to give a prokinetic agent such as domperidone or erythromycin, laxatives and occasionally, if there is a need for distal gut deflation, suppositories. It may be necessary to give feeds by continuous infusion. Milk-free diets can be used and in difficult cases full gastrointestinal investigation including upper and lower gastrointestinal endoscopy, barium radiology, pH studies and scintigraphy may be indicated. A number of children, particularly those with cerebral palsy, respond to milk exclusion using a hydrolysed protein formula feed as an alternative.

## **Methods of feed delivery**

### **Nasogastric tube feeding**

This is the most commonly used route for short-term (<6 weeks) enteral feeding given either by bolus or continuously. There is a risk of reflux and aspiration pneumonia. Nasal irritation and inhibition of oral feeding sometimes occur. Most infants will not tolerate nasogastric feeding long term.

### **Nasojejunal feeding**

This is indicated when nasogastric feeding is not tolerated because of delayed gastric emptying or gross gastro-oesophageal reflux. Feed usually needs to be given continuously to avoid dumping. If nasojejunal feeding is required long term a gastrojejunal tube or jejunostomy can be fashioned.

### **Gastrostomy tube feeding**

Gastrostomy is probably the best route for long-term (>6 weeks) feeding. Gastrostomy tubes are commonly inserted endoscopically (percutaneous endoscopic gastrostomy). They can also be inserted laparoscopically, surgically and under fluoroscopic control (by an interventional radiologist). The complications are few including small risk of bleeding, infection, leaking, dislodgement of the tube, over granulation and rarely worsening of reflux.

### **Indications for gastrostomy tube placement**

- Chronic disease with nutritional impairment, e.g. cystic fibrosis, bronchopulmonary dysplasia
- For nutritional therapy, e.g. Crohn disease

- Difficulties with feeding, e.g. cerebral palsy, particularly with an associated bulbar palsy. Some of these children may also have severe gastro-oesophageal reflux and require fundoplication
- Children long-term dependent upon nasogastric feeding for any other reason

### **Jejunal feeding – long term**

Long-term (>6 weeks) jejunal feeding can be considered in cases of severe reflux or delay in gastric emptying where surgery is not possible. This can be done by following methods:

- Jejunal tube insertion via PEG (percutaneous endoscopic gastrostomy)
- Percutaneous endoscopic jejunostomy
- Subcutaneous jejunostomy
- Surgical jejunostomy (e.g. roux-en-Y)

## **3.3 Parenteral nutrition**

There are differences between children and adults particularly in terms of nutritional reserve:

- Adults can survive 90 days without food
- Preterm infants of 1 kg can survive 4 days
- Preterm infants of 2 kg can survive 12 days
- Term infants of 3.5 kg can survive 32 days
- One year olds can survive 44 days

### **General principles of parenteral nutrition**

- Parenteral nutrition (PN) is usually indicated when a sufficient nutrient supply cannot be provided orally or enterally to prevent or correct malnutrition or to sustain appropriate growth
- It is, however, important to use the gut where possible
- The complete exclusion of luminal nutrients is associated with atrophic changes in the gut, reduced pancreatic function, biliary stasis and bacterial overgrowth
- It is not usually necessary to use PN for less than 5 days except in the extremely preterm infant
- It is important to evaluate risk of re-feeding syndrome before considering PN

### **Benefits of minimal enteral nutrition in children who are PN fed**

- Stimulation of mucosal adaptation (trophic feeding)
- Protection against sepsis (normalize flora)
- Improved bile flow with decreased risk of cholestasis
- Reduced time to establish enteral feeds

### **Indications for PN**

#### **Neonates**

### *Absolute indications*

- Intestinal failure (short gut, functional immaturity, pseudo-obstruction)
- Necrotizing enterocolitis

### *Relative indications*

- Hyaline membrane disease
- Promotion of growth in preterm infants
- Possible prevention of necrotizing enterocolitis

## **Older infants and children**

### *Intestinal failure*

- Short bowel syndrome
- Protracted diarrhoea
- Chronic intestinal pseudo-obstruction
- Postoperative abdominal or cardiothoracic surgery
- Radiation/cytotoxic therapy

### *Exclusion of luminal nutrients*

- Crohn disease

### *Organ failure*

- Acute renal failure or acute liver failure

### *Hypercatabolism*

- Extensive burns
- Severe trauma

## **Practical issues**

### **PN prescribing**

There are standard regimens for PN prescribing at different ages. This will include the starter regimen which then increases in nutrient density over the first few days. Protein is supplied as amino acid, carbohydrate as glucose and fat as a lipid emulsion. Electrolyte, calcium and phosphate contents need to be carefully controlled. Calorie density is increased through an increase in carbohydrate gradually over first few days. It is important to use standard regimens adjusted according to fluid balance, electrolyte status and tolerance, e.g. of increases in glucose. It is important not to push calorie density up too much without expert advice because this may result in poor tolerance and toxicity with a net reduction in metabolized energy intake. The use of a PN pharmacist together with a nutrition team is essential in difficult cases.

## **Monitoring during PN**

The initial frequency of biochemical monitoring will depend on the degree of electrolyte impairment and other factors, e.g. sepsis, liver disease. It is especially important in poorly nourished children who are at risk of re-feeding syndrome. It is generally necessary in the acute situation to do at least routine biochemistry (including blood glucose, phosphate, magnesium and urine dipstick) daily until stable and then twice weekly. Urine electrolytes should be monitored twice weekly at least initially. Liver function, calcium and phosphate should be done weekly. Trace metals (copper, zinc, selenium, magnesium) should be checked monthly. In children on long-term PN 6-monthly iron status, vitamin B<sub>12</sub>, red cell folate, fat-soluble vitamins, aluminium and chromium should be measured. Chest radiograph, liver ultrasonography and echocardiography should be done 6- to 12-monthly.

Blood glucose should be monitored frequently during periods of increasing carbohydrate load.

## **Complications**

### **Complications associated with use of PN**

- Phlebitis
- Infection
- Hypo- and hyperglycaemia, hypophosphataemia
- Electrolyte disturbance
- Fluid overload
- Anaemia
- Trace element deficiencies
- Vitamin deficiencies
- Essential fatty acid deficiency
- Cholestasis and hepatic dysfunction
- Metabolic acidosis
- Hypercholesterolaemia
- Hypertriglyceridaemia
- Granulomatous pulmonary arteritis

### **Complications associated with central venous catheter insertion**

- Sepsis
- Air embolism
- Arterial puncture
- Arrhythmias
- Chylothorax
- Haemothorax
- Pneumothorax
- Haemo-/hydropericardium
- Malposition of catheter
- Central venous thrombosis
- Thromboembolism

- Extravasation from fractured catheter
- Tricuspid valve damage
- Catheter tethering

### **Central venous catheter-related bloodstream infection**

Central venous catheter (CVC) infections are the most common and potentially life-threatening complication associated with PN. Coagulase-negative staphylococcal infection is the most common. A child on PN should have cultures taken (both central and peripheral) and broad-spectrum antibiotics started promptly if the temperature is more than 38.5°C or there are other strong indications of sepsis. It is important that appropriate procedures are in place to ensure that lines are dealt with aseptically and only by trained personnel. Long-term feeding lines should not, for example, be used for blood letting. Antibiotic locks can be used once the sensitivities are available and treatment is continued for at least 10–14 days. Removal of a CVC is considered in patients presenting with overwhelming sepsis or shock, and those with persistent positive cultures (colonized lines) despite appropriate antibiotic treatment.

Children with short gut/enteropathy are at highest risk because of bacterial translocation; they should have regular gut decontamination, particularly if infections are frequent.

### **Occlusion of a CVC**

This can be partial or complete occlusion. Partial occlusion can be resolved through prompt intervention to unlock the line by checking for external occlusion (clamps or kinks in the tubing) or flushing the CVC with saline/heparin sodium (10 U/ml) using strict aseptic technique. Smaller size syringe (5 ml/2 ml) can be used to deliver greater pressure. If this fails, an unblocking agent such as urokinase/alcohol/hydrochloric acid can be used. Rarely, a CVC is completely occluded and needs to be removed.

### **PN-associated liver disease**

PN-associated liver disease (PNALD) develops in 40–60% of infants who require long-term PN for intestinal failure. The clinical spectrum includes cholestasis, cholelithiasis, hepatic fibrosis with progression to biliary cirrhosis, and the development of portal hypertension and liver failure. The pathogenesis is multifactorial and is related to prematurity, low birthweight and duration of PN. The degree and severity of the liver disease is related to recurrent sepsis, including catheter sepsis, bacterial translocation and cholangitis. Lack of enteral feeding leading to reduced gut hormone secretion, reduction of bile flow, and biliary stasis are important mechanisms in the development of cholestasis, biliary sludge and cholelithiasis. The management strategies for the prevention of PN-induced liver disease include early enteral feeding, a multidisciplinary approach to the management of parenteral nutrition, and aseptic catheter techniques to reduce CVC-related bloodstream infection (CRBSI). Cyclical PN, use of reduced intravenous fat intake and empirical change to different lipid emulsion (SMOF) can help reduce progression of PNALD. The administration of ursodeoxycholic acid may improve bile flow and reduce gallbladder and intestinal stasis. Fat-soluble vitamin replacement is essential by the intravenous route when child is parenterally fed, but may be given orally with regular monitoring during the transition to oral/enteral feeding.



# Consequences of trace element abnormalities described during parenteral nutrition

Trace element	Deficiency	Excess
Zinc	Periorofacial dermatitis Immunodeficiency Diarrhoea Growth failure	
Copper	Refractory hypochromic anaemia Neutropenia Osteoporosis Subperiosteal haematoma Soft tissue calcification	
Selenium	Cardiomyopathy Skeletal myopathy, pain and tenderness Pseudoalbinism	
Chromium	Glucose intolerance Peripheral neuropathy Weight loss	Renal and hepatic impairment
Manganese	Lipid abnormalities Anaemia	Liver toxicity Damage to basal ganglia
Molybdenum	Tachycardia Central scotomas Irritability Coma	
Aluminium		Anaemia Osteodystrophy Encephalopathy

## 3.4 Re-feeding syndrome

Re-feeding syndrome is a potential metabolic complication in any malnourished patient which can happen with enteral or parenteral nutrition. This happens as a consequence of severe fluid and electrolyte shifts, which can cause disturbances in body systems including cardiac arrhythmias. Before feeding it is important to assess nutritional status and hydration, cardiac status, serum electrolytes, magnesium and phosphate. The greatest vigilance is required especially in the first week of feeding. Patients at risk of re-feeding syndrome usually have feeds introduced gradually over the first 48 hours with careful monitoring of electrolytes, calcium, urea, creatinine, phosphate and magnesium. Feeds are subsequent increased over the next 5–7 days with supplementation if necessary.

### Risk factors for re-feeding syndrome

#### One or more

- BMI <16
- Unintentional weight loss >15% in 3–6 months
- $\geq 10$  days with little or no nutritional intake
- Low magnesium, potassium or phosphate before feeding

#### Two or more

- BMI <18.5
- Unintentional weight loss >15% in 3–6 months
- ≥5 days with little or no nutritional intake
- Alcohol misuse, chronic diuretic, antacid, insulin use or chemotherapy

## 3.5 Intestinal failure

Intestinal failure is defined as ‘a reduction in the functioning intestinal mass below the amount necessary for adequate absorption to allow for growth’. Management of intestinal failure has been revolutionized in last five decades by the availability of PN, advances in neonatal intensive care and paediatric surgical techniques with increase in survival of children with intestinal failure.

### Aetiology

#### Short bowel syndrome

See below.

#### Motility disorders

An example of this is chronic idiopathic intestinal pseudo-obstruction syndrome. This is a group of rare disorders that present with signs and symptoms of intestinal obstruction in the absence of identifiable mechanical obstruction. These disorders usually present in infancy and death or dependence on PN is common.

#### Mucosal disorders

These disorders present in early life with intractable diarrhoea. They can be primary epithelial abnormalities such as microvillus inclusion disease, tufting enteropathy and glycosylation disorder, immune-mediated mucosal disorders such as underlying immune deficiencies (e.g. severe combined immunodeficiency), autoimmune enteropathy and syndromic diarrhoea. Most of these children are long-term PN dependent and ultimately need consideration of small bowel transplantation.

#### Short-bowel syndrome

This is defined as intestinal failure secondary to massive resection of the diseased gut or as a consequence of congenital bowel abnormality. The consequence are inadequate absorption of fluids, electrolytes and nutrients from the bowel.

#### Aetiologies

- Neonatal – necrotizing enterocolitis, intestinal atresia, volvulus, gastroschisis and total aganglionosis
- Older child – trauma, Crohn disease requiring resection of bowel, vascular abnormalities, tumour, radiation enteritis and mesenteric infarction.

## **Factors that determine outcome in short-bowel syndrome**

- Length of bowel resected and remaining bowel length – preterm bowel is likely to undergo further growth (bowel length increases by 100% in the third trimester)
- Less than 40 cm of residual small bowel in infancy is usually associated with a need for long-term nutritional support
- Quality of bowel remaining – ischaemic, distended, ileum greater potential to adapt than jejunum
- Presence of ileocaecal valve – loss of ileocaecal valve results in faster transit. Backflow (loss of the one-way valve) makes bacterial overgrowth more likely
- Improved outcome if colon still present
- Coexistent disease, e.g. enteropathy is an adverse risk factor
- Presence of intestinal failure-associated liver disease (IFALD) is an adverse risk factor
- Failure to achieve full enteral feeding after 5 years of PN suggest lifelong dependency on PN

## **Management**

1. Maintenance of normal growth through adequate calorie, nutrient and micronutrient intake given through PN. Careful clinical and biochemical monitoring is essential. Home PN is considered as soon as clinical stability is achieved
2. Use of enteral feeding when gut function allows to help intestinal adaptation. There are three phases of intestinal adaptation: acute (PN-dependent, postoperative ileus), adaptive (increasing enteral nutrition, can take months to years) and chronic. The early introduction of enteral feeds promotes intestinal adaptation and will improve subsequent feed tolerance. Feeds are usually best given as a continuous infusion in the first instance and should be increased only if tolerated, i.e. no diarrhoea (or excess stoma output if present). PN should not be weaned until feed is tolerated and absorbed. Weight needs careful monitoring during weaning of PN
3. Minimizing risk of complications of gut failure and nutritional support
4. Optimizing quality of life: multidisciplinary management is required, including attention to the child's oral skills, social and psychological development and the needs of the family.
5. Non-transplantation surgery (bowel-lengthening procedures): aim is to provide maximum mucosal contact without disturbing motility or reducing total absorptive mass. Entire length of the bowel available is used. The Bianchi (bowel lengthening) procedure, intestinal tapering or plication and, recently, the serial transverse enteroplasty procedure (STEP) have been tried with varying success
6. Isolated liver transplantation – considered in those patients with short gut who have at least 30 cm of residual small bowel, have previously tolerated 50% of their estimated enteral feeds and demonstrated weight gain, but failed to achieve maximal adaptation because of end-stage liver disease
7. Intestinal transplantation (ITx) has emerged as a life-saving option for patients with intestinal failure who develop major complications. The indications for ITx are irreversible intestinal failure and one of the following: impaired venous access (reduced to two suitable veins for placement of feeding catheters); progressive liver disease with coagulopathy, ascites and encephalopathy; and life-threatening episodes of catheter sepsis. This can be isolated small bowel transplantation or combined liver and small bowel transplantation

### 3.6 Home parenteral nutrition

Home PN is considered when it is anticipated that full enteral feeding would take more than 4 months to be established. Where possible PN is infused over 12 hours at night and a CVC is locked with heparinized saline in the day time. Parental motivation, suitable housing and adequate training by the multidisciplinary team looking after the child is extremely important. These patients need close follow-up to monitor their growth, tolerance to enteral feeds and biochemistry.

## 4. FOOD ALLERGY AND INTOLERANCE

Food allergy is one of the most common allergic disorders in the UK and its prevalence has increased dramatically in recent years. It is important to distinguish between allergy and intolerance. An allergy implies an immune-mediated reaction to food antigen (protein). Classically this is by IgE-mediated, type I hypersensitivity. The signs of this include anaphylaxis, urticaria and atopic dermatitis. Allergy can be non-IgE mediated which is characterized by delayed or non-acute onset and implies intolerance. Rarely it can present as a mixed reaction involving both IgE and non IgE responses. Intolerance does not necessarily need to be to a protein and includes, for example, lactose intolerance.

The National Institute for Health and Clinical Excellence (NICE) has recently produced clinical guidelines for diagnosis and assessment of food allergy in children and young people in primary care and community settings (February 2011).

### 4.1 Cows' milk protein intolerance

Cows' milk protein intolerance (CMPI) is the clinical syndrome resulting from sensitization to one or more proteins in cows' milk.

#### Clinical spectrum of cows' milk protein intolerance

- Acute type 1-mediated hypersensitivity
- Delayed-onset hypersensitivity
- Cows' milk allergic oesophagitis (eosinophilic)
- Cows' milk-sensitive enteropathy
- Cows' milk allergic colitis (eosinophilic)
- Non-specific symptoms possibly attributable to cows' milk

Presentation is most commonly with gastrointestinal symptoms such as vomiting, diarrhoea, colic and constipation. Other rare presentations can be respiratory (wheeze, rhinitis, asthma), dermatological (atopic dermatitis, eczema, urticaria) and behavioural (irritability, crying and milk refusal).

Diagnosis is dependent on the clinical manifestations. A good history and, if possible, dietetic

assessment is essential. Skin-prick testing and IgE radioallergosorbent testing (RAST) are sometimes used but lack sensitivity or specificity. A negative result does not exclude allergy and a positive result can be seen in children who tolerate cows' milk protein without a problem. If either an enteropathy or colitis is suspected then it is useful to obtain histological confirmation.

## Management

- Milk exclusion with a milk substitute. Soya preparations are commonly used and are palatable. Soya products should not be used in infants aged <6 months because of the presence of phytoestrogens in soya milk. There is a cross-reactivity between cows' milk and soya protein of up to one-third and so extensively hydrolysed protein formula feeds are preferred. Minimum of 2–4 weeks' trial should be given. Risk of failure with extensively hydrolysed formula is 10% when amino acid-based feeds should be used. In exclusively breast-fed infants with suspected CMPI, mothers may need to exclude cows' milk from their diet
- It is common in children with milk allergy to see reactions to other foods, the most common of which are soya, egg, wheat and peanut. In the case of suspected multiple food allergy or severe reaction to CMP, a strict exclusion diet with amino acid-based formula should be considered
- The natural history of cows' milk intolerance is one of resolution with 80–90% back on a normal diet by their third birthday. It is sensible to challenge regularly. It is usual to organize challenges in hospital, particularly if the initial reaction was severe, because of the risk of anaphylaxis

## 4.2 Peanut allergy

Peanut and nut allergies are seen with increasing frequency. Between 60 and 80% of children with peanut allergy (peanuts are a vegetable rather than a nut) are also allergic to other nuts. Reactions vary from mild urticaria to life-threatening anaphylaxis. Skin-prick testing is useful with a high sensitivity and specificity. Peanut avoidance is difficult and dietetic support is essential. Cross contamination in food production is common. The natural history suggests that children with early-onset allergy may grow out of it, although allergy in older children with symptomatic reactions is more likely to persist. Active management involves challenging peanut skin-prick-negative children. This is clearly not without risk and needs to be done in an inpatient setting with facilities for resuscitation.

Common other nuts that cause allergic reactions include brazil nut, cashew nut, hazelnut, walnut, almond and pistachio nut.

## 4.3 Food-induced anaphylaxis (IgE mediated)

Children who have had an anaphylactic reaction are at increased risk of a second reaction after second exposure, for which there is a significant mortality. These children benefit from an adrenaline pen. It is important that such children and their families are taught properly about the indications for use of the pen and subsequent action that should be taken. The school and all the main carers need to

be involved. A MedicAlert bracelet is useful. Children should also have antihistamines kept in their house. These are appropriate for minor reactions and some units advocate their use before potential accidental exposure.

It is essential to be aware of the guidelines for the management of an anaphylactic reaction. Please refer to the APLS anaphylaxis algorithm (November 2009) by the Advanced Life Support Group (ALSG) (see [www.doh.gov.za/docs/immunization/anaphylaxis.pdf](http://www.doh.gov.za/docs/immunization/anaphylaxis.pdf)).

## 4.4 Carbohydrate intolerance

### Disorders of disaccharide absorption

#### Primary

- Congenital alactasia
- Congenital lactose intolerance
- Sucrose–isomaltase deficiency

#### Secondary (acquired)

- Post-enteritis (rotavirus), neonatal surgery, malnutrition
- Late-onset lactose intolerance

### Disorders of monosaccharide absorption

#### Primary

- Glucose–galactose malabsorption

#### Secondary (acquired)

- Post-enteritis, neonatal surgery, malnutrition

### Lactose intolerance

This is usually acquired, most commonly post-rotavirus infection. The deficient enzyme is the brush-border enzyme lactase, which hydrolyses lactose into glucose and galactose. The intolerance will characteristically present with loose explosive stools. The diagnosis is made by looking for reducing substances in the stool after carbohydrate ingestion. Formal confirmation of the specific offending carbohydrate is through stool chromatography. Treatment is with a lactose-free formula in infancy and a reduced lactose intake in later childhood.

### Glucose–galactose malabsorption

This is a rare, autosomal recessively inherited condition, characterized by rapid-onset watery diarrhoea from birth. It responds to withholding glucose (stopping feeds) and relapses on reintroduction. The diagnosis is essentially a clinical one. Reducing substances in the stool will be positive. Small-bowel biopsy and disaccharide estimation will be normal. Treatment is by using fructose as the main carbohydrate source.

### **Sucrase–isomaltase deficiency**

This is a defect in carbohydrate digestion, with the enzyme required for hydrolysis of sucrose and alpha-limit dextrins not present in the small intestine. Symptoms of watery diarrhoea and/or faltering growth develop after the introduction of sucrose or complex carbohydrate into the diet.

- Symptoms can be very mild
- Reducing substances in the stool are negative (non-reducing sugar)

Diagnosis is by stool chromatography. Management is by removal of sucrose and complex carbohydrate from the diet.

### **Hydrogen breath testing**

The hydrogen breath test looks for carbohydrate malabsorption. Lactose is the usual substrate. The principle is that malabsorbed carbohydrate will pass to the colon where it is metabolized by bacteria and hydrogen gas is released. The gas is then absorbed and released in the breath. If there is a peak it suggests carbohydrate malabsorption. Other carbohydrates can be given as the substrate.

## **5. GASTRO-OESOPHAGEAL REFLUX**

Gastro-oesophageal reflux (GOR) is common and implies non-forceful regurgitation of milk and other gastric contents into the oesophagus (regurgitation). It is a normal physiological phenomenon. It is common in infancy and is also seen in older children and adults, particularly after meals.

Functional reflux is regurgitation without morbidity or clinical signs suggestive of gastro-oesophageal reflux disease.

### **Gastro-oesophageal reflux disease**

Gastro-oesophageal reflux disease (GORD) is defined as ‘gastro-oesophageal reflux associated with troublesome symptoms or complications’. It refers to reflux with significant morbidity including faltering growth, respiratory disease and oesophagitis, or complications of oesophagitis such as stricture.

### **Differential diagnosis of GOR**

- Infection, e.g. urinary tract infection, gastroenteritis, peptic ulcer disease
- Intestinal obstruction, e.g. pyloric stenosis, malrotation, intestinal atresia
- Food allergy and intolerances, e.g. cows' milk allergy, soy allergy, coeliac disease
- Eosinophilic oesophagitis
- Metabolic disorders, e.g. diabetes, inborn errors of metabolism
- Psychological problems, e.g. anxiety, irritable bowel syndrome
- Intestinal dysmotility, e.g. primary, achalasia, secondary to neurodisability
- Drug-induced vomiting, e.g. cytotoxic agents
- Primary respiratory disease, e.g. asthma, cystic fibrosis
- Rumination

## Symptoms and signs of GORD

### Typical

- Excessive regurgitation/vomiting
- Nausea
- Weight loss/faltering growth
- Irritability with feeds, arching, colic/food refusal
- Dysphagia
- Chest/epigastric discomfort
- Excessive hiccups
- Anaemia – iron deficiency
- Haematemesis/melaena
- Aspiration pneumonia
- Oesophageal obstruction due to stricture

### Atypical

- Wheeze/intractable asthma
- Cough/stridor
- Apnoea/apparent life-threatening events/sudden infant death syndrome
- Cyanotic episodes
- Generalized irritability
- Sleep disturbance
- Neurobehavioural symptoms – breath-holding, Sandifer syndrome, seizure-like events
- Worsening of pre-existing respiratory disease
- Secondary, e.g. post-surgery

## Investigation of GOR

Physiological reflux is common and resolves with symptomatic treatment. Full clinical assessment and consideration of differential diagnosis are essential. Parental reassurance is all that is needed in



most cases. Severe cases need investigations and may need further assessment by multidisciplinary team involving a dietician, speech and language therapist, paediatric gastroenterologist and paediatric surgeon.

### **Barium radiology**

This assesses the patient over only a short period and therefore may either miss pathological reflux or overdiagnose physiological reflux. It is a good test to pick up anatomical abnormalities associated with recurrent vomiting, such as malrotation, duodenal web.

### **A pH study**

This is considered the ‘gold standard’ for acid reflux.

#### *Specific indications for pH study*

- Diagnostic uncertainty
- Poor response to medical treatment
- If surgery is being considered
- Children in whom doing the test will lead to a change in management
- Symptoms suggestive of occult reflux
- Unexplained or difficult-to-control respiratory disease

The most sensitive marker of acid reflux on pH study is the reflux index (percentage of time pH <4).

The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) consensus recommendation is that a reflux index >7% is abnormal:

- Mild reflux up to 10%
- Moderate reflux 10–20%
- Severe 20–30%

There are several limitations to a pH study such as it is unable to detect anatomical abnormalities or aspiration and alkaline reflux. Reproducibility is poor. Severity of pathological acid reflux does not correlate with symptom severity and complications such as degree of oesophagitis.

### **Nuclear medicine ‘milk’ scan**

This is used to assess acid or alkali reflux after a physiological meal, assess gastric emptying and it is possible to make a 24-hour film to look for evidence of aspiration (technetium-99m radioscintigraphy)

### **Oesophageal impedance**

This measures the changes in the electrical impedance (resistance) between multiple electrodes located along an oesophageal catheter. The impedance changes suggestive of retrograde bolus movement indicate reflux. This test is superior to pH monitoring alone for evaluation of the temporal relationship between symptoms and GOR.

### **Oesophageal manometry**

This measures the pressure inside the lower part of the oesophagus. It may be abnormal in patients with GORD but the findings are not sufficiently sensitive or specific to confirm the diagnosis, or to predict response to medical or surgical therapy. It is useful to confirm a diagnosis of achalasia or other motor disorders of the oesophagus that may mimic GORD.

### **Upper gastrointestinal endoscopy with biopsy**

A useful investigation in children with severe symptomatic reflux with suspected oesophagitis. An eosinophilic infiltrate in oesophageal biopsies is characteristic of reflux oesophagitis. However, an excess of eosinophils suggests cows' milk allergic oesophagitis/eosinophilic oesophagitis. Normal oesophageal histology does not exclude GOR.

## **Management of GOR**

### **Step-up approach to the treatment of GOR**

- Step 1 – lifestyle changes
- Step 2 – antacids/thickeners/H<sub>2</sub>-receptor blockers/?prokinetics
- Step 3 – proton pump inhibitors
- Step 4 – add prokinetics if not already tried/consider change in diet/feed regimen
- Step 5 – surgery

### **Simple measures**

#### *Infants*

- Functional reflux does not require specific treatment
- Explanation and reassurance
- Review of feeding posture
- Review of feeding practice, e.g. too frequent feeds, large-volume feeds
- Use of feed thickeners or an anti-reflux milk
- Cows' milk allergy is a potential differential and infants with persistent reflux may benefit from a 2–4 weeks' trial of extensively hydrolysed formula.

#### *Older children*

- Lifestyle and diet
- Avoid excess fat, chocolate, tea, coffee, gaseous drinks
- Avoid tight-fitting clothes

### **Specific treatment**

Indicated in children with severe symptomatic reflux suggestive of GORD. Acid suppression agents are the mainstay of the treatment. It is important to balance benefit of treatment with potential adverse effects of acid suppression, including increased risk of community-acquired pneumonia and gastrointestinal infections.

## **Compound alginates (e.g. Gaviscon)**

These react with gastric acid to form a viscous gel.

## **Acid suppression**

H<sub>2</sub>-receptor blockers, e.g. ranitidine, are widely used and well tolerated. Oral ranitidine provides symptomatic relief and endoscopic improvement of oesophagitis in children with GORD.

Proton pump inhibitors, e.g. omeprazole, lansoprazole, increase the pH of gastric content, decrease the total volume of secretions and facilitate emptying. Superior to histamine-receptor blockers in healing erosive oesophagitis. Also effective in children with GORD resistant to histamine-receptor blockers.

## **Prokinetic drugs**

These drugs increase lower oesophageal sphincter pressure, improve oesophageal clearance and promote gastric emptying:

- Metoclopramide
- Domperidone
- Erythromycin

## **Other agents**

- Buffering agents (magnesium hydroxide and aluminium hydroxide) are useful for occasional heartburn but long-term use is associated with significant risk of toxicity
- Sucralfate binds to inflamed mucosa and forms a protective layer that resists further damage from gastric acid

## **Children with severe reflux resistant to medical management**

They may benefit from:

- Trial of hydrolysed protein formula feed
- Period of continuous feeding
- Trial of gastrostomy/gastrojejunal feeding

## **Surgery**

It is required for reflux resistant to medical treatment. It is essential to rule out non-GORD causes of symptoms before considering surgery.

## **Indications for surgery**

- Failure of optimal medical therapy
- Dependence on long-term medical therapy
- Extraoesophageal manifestation (asthma, cough, chest pain, recurrent pulmonary aspiration of refluxate)

- Complication of GORD (e.g. Barrett oesophagus, peptic stricture)

Surgery is usually fundoplication with consideration of a pyloroplasty if there is delayed gastric emptying. A gastrostomy for feeding is often done at the same time, particularly if there are feeding problems, e.g. neurodisability. Most fundoplications are done laparoscopically these days with reduced postoperative complications, reduced hospital stay and good long-term outcome. Potential complications of surgery are recurrence of reflux (10%), bloating, dumping and intestinal obstruction.

## 5.1 Differential diagnosis of reflux oesophagitis

- Cows' milk allergic oesophagitis
- Eosinophilic oesophagitis
- Candidal oesophagitis
- Chemical oesophagitis from caustic ingestion
- Achalasia
- Crohn disease

## 5.2 Feeding problems in neurodisability

Feeding difficulties in children with neurodisability are common and there are many potential causes.

Children require careful multidisciplinary assessment by a feeding team including a dietician, speech and language therapist, occupational therapist and neurodevelopmental paediatrician.

### Relevant issues to consider

- Bulbar weakness with oesophageal incoordination
- Primary or secondary aspiration
- Reflux oesophagitis
- Widespread gut dysmotility
- Mobility and posture, degree of spasticity
- Nutritional state
- Constipation

Attention to nutrition is of key importance and many children benefit from a feeding gastrostomy with or without fundoplication.

Gastro-oesophageal reflux disease is common and should be treated aggressively.

Gut dysmotility may be an important factor in these patients often resulting in delayed gastric emptying, which can significantly impact on the ability to feed. This can present as bloating, constipation and abdominal pain, and must be carefully evaluated. Possible therapeutic interventions

include prokinetic agents, laxatives and rarely suppositories.

## 5.3 Eosinophilic oesophagitis

Eosinophilic oesophagitis (EO) is an important differential diagnosis of GOR that presents with similar symptoms but fails to respond to conventional acid blockade therapy. In older children, dysphagia and food impaction can occur. It is more commonly seen in patients with atopy or in those with a family history of atopic disease. Diagnosis is based on endoscopic findings with characteristic histology.

Standardised skin-prick testing and RAST are not generally informative.

Treatments include those for GOR, trial of dietary elimination, inhaled corticosteroids (swallowed), anti-inflammatories and immunosuppressants. There is a natural history of relapse, remission and chronicity.

## 5.4 Achalasia

This is a motility disorder where the lower oesophageal sphincter fails to relax in response to swallowing. It presents typically in late childhood/adult life and clinical features include dysphagia, regurgitation, cough and chest discomfort. It is an important differential of GORD presenting in older children. It can develop as a complication of antireflux surgery. There is an increased risk of oesophageal carcinoma in untreated achalasia.

Diagnosis is by barium radiology, which shows the fluid level and 'rat-tail appearance' of narrow distal oesophagus. Oesophagoscopy and biopsies can be done if oesophagitis is suspected. Manometry can be useful.

Treatment options are balloon dilatation of the lower oesophageal sphincter and the Heller myotomy. Botulinum toxin has been used.

## 5.5 Dysphagia

Dysphagia – means difficulty in swallowing:

- It can cause coughing or choking on swallowing, inability to swallow, pain on swallowing, regurgitation of food or feeling of something 'stuck' in the throat
- Long-term effects could be faltering growth and repeated chest infections secondary to aspiration events
- Causes could be organic or functional:
  - Organic causes – deformity in the oropharynx or infection of nerves or muscles responsible for

swallowing. Cerebral palsy is the most common cause of dysphagia due to neuromuscular weakness. In achalasia and scleroderma, muscles of the oesophagus are affected and there is difficulty pushing the food forward in stomach. Severe GORD can also present as dysphagia, as can eosinophilic oesophagitis

- Functional causes – children with learning difficulties and developmental delay can present with dysphagia. Oral aversion and lack of oral feeding experience due to prolonged nasogastric feeding in early life can be a factor

- Investigation and treatment depend on the underlying cause. Assessment by dietician and speech and language therapist is extremely helpful

## 6. PEPTIC ULCER DISEASE

### 6.1 *Helicobacter pylori* infection

*Helicobacter pylori* is a Gram-negative bacterium. Infection is usually acquired in childhood. Prevalence rates are, however, very variable. Persistent infection causes a chronic gastritis which may be asymptomatic. There is a strong relationship between helicobacter infection and peptic ulceration in both adults and children. There is no proven association between helicobacter infection and recurrent abdominal pain. Transmission is faeco-oral and familial clustering is common. Investigations are considered in children with symptoms suggestive of peptic ulcer disease and depends on the clinical picture, local prevalence and tests available.

Diagnosis is by the following:

- Stool antigen testing – highly sensitive and specific. Need to stop antibiotics and antacids before the test
- Serology – less specific, with high false-positive rates. Negative test excludes infection. Usually reverts to negative within 6–12 months of treatment
- Rapid urease tests –  $^{13}\text{C}$  breath test, CLO (*Campylobacter*-like organism) test
- Endoscopy allows detection of ulcer as well as gastritis/oesophagitis. Histology as well as the CLO test on biopsy specimens can be diagnostic but culture has low yield.

There are various treatment regimens and the reader is referred to the *British National Formulary* for children for the most up-to-date regimen. Acid inhibition with antibiotic treatment is used. There is usually no need to continue antacid treatment further unless the ulcer is large or complicated by haemorrhage or perforation. Reinfection can occur. Treatment failure usually indicates resistance, reinfection within families or institutions, or poor compliance.

### 6.2 Other causes of antral gastritis and peptic ulceration

- Anti-inflammatory drugs
- Crohn disease

- Zollinger–Ellison syndrome
- Autoimmune gastritis (adults)

## 6.3 Zollinger–Ellison syndrome

Gastrin-producing tumour of the endocrine pancreas, presenting with gastric acid hypersecretion and resulting in fulminant and intractable peptic ulcer disease.

## 7. CHRONIC DIARRHOEA

Chronic diarrhoea refers to diarrhoea that has persisted for more than 2–3 weeks. Children with chronic diarrhoea and faltering growth need investigation, because the underlying cause may be a malabsorption. Examination of stool is essential as a part of the clinical assessment.

### Common causes

- Infections including post-enteritis syndrome
- Coeliac disease (see [Section 8](#))
- Food intolerance (see [Section 4](#))
- Bacterial overgrowth
- Short-bowel syndrome (see [Section 3.5](#))
- Protein-losing enteropathy
- Pancreatic insufficiency, e.g. cystic fibrosis, Schwachman–Diamond syndrome
- Inflammatory bowel disease (see [Section 10](#))
- Drug induced, e.g. antibiotics, laxatives

### Rare causes

- Congenital diarrhoeas/intractable diarrhoea of infancy
- Intestinal lymphangiectasia
- Abetalipoproteinaemia (see [Section 2.8](#))
- Immunodeficiency

In children with *chronic diarrhoea who are thriving* the following alternative diagnoses should be considered:

- Constipation with overflow (see [Section 13](#))
- Toddler’s diarrhoea (chronic non-specific diarrhoea of childhood)
- Carbohydrate intolerance (see [Section 4.4](#))
- Irritable bowel syndrome

### Red flags in the history and examination for further investigation

- Poor weight gain/weight loss
- Continuous diarrhoea
- Night stools
- Acid stools
- Blood and mucus in the stools
- Faltering growth
- Associated symptoms suggestive of systemic disease – fever, rash, arthritis

## 7.1 Congenital diarrhoea/intractable diarrhoea of infancy

This refers to persistent diarrhoea starting at birth with four or more stools per day and faltering growth. The following are examples.

### **Congenital microvillous atrophy (microvillous inclusion disease)**

Intractable diarrhoea with poor weight gain present from birth. Poor tolerance of even minimal enteral intake. Pathology is ultrastructural abnormality at the microvillous surface. Patients have long-term PN dependence with poor survival rate. Intestinal transplantation offers a potential cure.

### **Tufting enteropathy**

Presentation is similar to microvillous inclusion disease. There is a primary intestinal epithelial dysplasia with the presence of ‘tufts’ of extruding epithelial cells on biopsy. They are PN dependent in early life; however, there is a potential to tolerate some enteral feeds as intestinal function improves with age. They can have associated problems such as choanal atresia, oesophageal atresia, imperforate anus, short stature, delayed bone age and non-specific punctate keratitis.

### **Glucose–galactose malabsorption (see [Section 4.4](#))**

### **Congenital chloride diarrhoea**

Rare autosomal recessive condition. Severe watery diarrhoea starting at birth often with a past history of polyhydramnios. There is a failure of chloride reabsorption (in exchange for bicarbonate) in the ileum. Serum sodium and chloride are low with metabolic alkalosis. Stool pH and stool chlorides are high (>90 mmol/l). Treatment is with sodium and potassium chloride supplements. Prognosis is good if the diagnosis is made early.

### **Autoimmune enteropathy**

Protracted diarrhoea presenting in infancy associated with the presence of circulating autoantibodies against intestinal epithelial cells. There is partial villous atrophy with an inflammatory infiltrate on small bowel biopsy. Associated with other autoimmune conditions (IPEX syndrome – immune dysregulation, polyendocrinopathy, enteropathy, X-linked). Treatment is with nutritional support and immunosuppression.



## 7.2 Post-enteritis syndrome

This is diarrhoea post-gastroenteritis that continues for more than 3 weeks with poor weight gain or weight loss. It is usually seen in infants. Potential causes can be continuing infection, further infection, carbohydrate intolerance or enteropathy presenting as a severe malabsorptive syndrome (secondary to either initial infection or unmasking underlying pathology, e.g. coeliac disease, CMPI, cystic fibrosis). Treatment of associated condition usually suffices in most cases. Occasionally it can be severe and need a period of bowel rest with parenteral nutrition.

## 7.3 Cows' milk protein-sensitive enteropathy

This implies enteropathy secondary to cows' milk protein and improves after withdrawal of cows' milk protein with a longer-term history of resolution in most cases (see [Section 4.1](#)).

## 7.4 Giardiasis

*Giardia* sp. is a protozoal parasite that is infective in the cyst form, and found in contaminated food and water. Clinical manifestations vary; it can be asymptomatic, acute diarrhoeal disease or chronic diarrhoea. Diagnosis is by stool examination for cysts or examination of the duodenal aspirate on endoscopy. Treatment is with metronidazole and is often given blind in suspicious cases.

## 7.5 Exocrine pancreatic insufficiency

Presents as chronic diarrhoea secondary to fat malabsorption. Diagnosis is suggested by the presence of fat in stool (steatorrhoea). Faecal elastase  $<150\mu\text{g/g}$  is suggestive of exocrine pancreatic insufficiency (false positive if stool is watery). Treatment is by pancreatic enzyme replacement.

Important causes are:

- Inherited disorders – cystic fibrosis, Schwachman–Bodian–Diamond syndrome, Pearson syndrome, Johanson–Blizzard syndrome, hereditary pancreatitis
- Pancreatitis – idiopathic, traumatic, viral, drug induced, nutritional and autoimmune
- Post-pancreatic surgery
- Crohn disease, coeliac disease, primary sclerosing cholangitis
- Autoimmune conditions (systemic lupus erythematosus)
- Anatomical abnormalities – pancreatic agenesis/hypoplasia

## Cystic fibrosis

This subject is well covered in the Respiratory Chapter 22. It is important to remember the gastrointestinal manifestations.

## **Gastrointestinal manifestations of cystic fibrosis**

### *Pancreatic*

- Insufficiency occurs in up to 90%
- Pancreatitis
- Abnormal glucose tolerance in up to 10% by the second decade
- Diabetes mellitus

### *Intestinal*

- Meconium ileus
- Atresias
- Rectal prolapse
- Distal obstruction syndrome
- Strictures, perhaps secondary to high-dose pancreatic supplementation

### *Hepatobiliary*

- Cholestasis in infancy
- Fatty liver
- Focal biliary fibrosis
- Multilobular cirrhosis

### *Abnormalities of the gallbladder*

- Cholelithiasis
- Obstruction of the common bile duct

## **Schwachman–Bodian–Diamond syndrome**

A rare autosomal recessive condition, the gene responsible is located on the long arm of chromosome 7 at position 7q11. Incidence of 1:20 to 1:200 000

Main features are pancreatic insufficiency, neutropenia and short stature. Other features include metaphyseal dysostosis, hepatic dysfunction, increased frequency of infections, and haematological abnormalities (including thrombocytopenia, increased risk of leukaemia)

## **7.6 Bacterial overgrowth (small bowel)**

Malabsorption with steatorrhoea and fat-soluble vitamin malabsorption can occur as a consequence of bacterial overgrowth. Risk factors include previous gastrointestinal surgery, strictures and short-bowel syndrome, particularly if there is loss of the ileocaecal valve. Repeated courses of antibiotics also are a risk factor. Treatment involves management of the underlying cause. Metronidazole, which is effective orally and intravenously, is the antibiotic of first choice. Probiotics have been used.

## 7.7 Intestinal lymphangiectasia

Functional obstruction of flow of lymph through the thoracic duct and into the inferior vena cava. Leads to fat malabsorption and a protein-losing enteropathy. It can be primary (congenital disorder of the lymphatic system) or secondary (pancreatitis, pericarditis, post-Fontan procedure or malignancy). Small bowel biopsies show patchy areas of dilated lymphatics in the absence of other pathology. Treatment is with medium-chain triglycerides – absorbed directly into the portal vein.

## 7.8 Protein-losing enteropathy

Refers to excess loss of protein from the gut secondary to altered permeability or lymph stasis or a combination of the two. It can happen as a feature of number of disease processes presenting as chronic diarrhoea. Investigation is directed to the likely underlying cause, based on history and examination. Serum albumin is low and stool  $\alpha_1$ -antitrypsin is generally raised

## 7.9 Chronic non-specific diarrhoea of childhood (toddler's diarrhoea)

Children tend to pass frequent, often explosive, loose stools with undigested food particles, which leads to significant anxiety. There are no additional features such as weight loss, abdominal pain, night stools or blood in the stools. Possible aetiology includes gut immaturity, dysmotility, emotional stress, excess fructose-containing juices/sorbitol/fibre in the diet and incomplete rectal evacuation. Management is by reassurance and avoidance of potential triggers.

## 8. COELIAC DISEASE

Coeliac disease is a reversible immune-mediated enteropathy of the small intestinal mucosa that involves heightened immunological response to ingested gluten (from wheat, barley or rye) in genetically susceptible people.

Prevalence is 1% when populations are screened. There are associations with HLA-DQ2 and -DQ8. There is an increased incidence in first-degree relatives.

Clinical presentation: coeliac disease presents anytime after gluten is introduced in to the diet (usually after 6 months).

- Classic phenotype (minority) – presents in early childhood with chronic diarrhoea, abdominal distension, faltering growth, pallor and irritability after introduction of gluten-containing foods to the diet
- Children presenting with gastrointestinal symptoms – presentation in late childhood with more

insidious symptoms related to the bowel such as abdominal pain, intermittent diarrhoea, constipation, vomiting, flatulence, anorexia and abdominal distension

- Children presenting with non-gastrointestinal symptoms

## **Non-gastrointestinal manifestations of coeliac disease**

- Dermatitis herpetiformis
- Osteoporosis/rickets/osteomalacia
- Iron deficiency anaemia
- Prolonged fatigue/lethargy
- Unexplained alopecia
- Delayed puberty/short stature
- Infertility/recurrent abortions/amenorrhoea
- Recurrent aphthous stomatitis
- Faltering growth
- Unexplained neurological symptoms, e.g. ataxia, irritability, neuropathies, migraine

## **Asymptomatic children diagnosed by target screening of the high-risk groups**

Risk factors for the development of coeliac disease with estimated lifetime prevalence (if known)

NICE Guideline CG86 advises offering screening if present:

- Autoimmune thyroiditis 7–15%
- Type 1 diabetes mellitus 2–10%
- Irritable bowel syndrome 7–11%
- Dermatitis herpetiformis 69–89%
- First-degree relatives of patients with coeliac disease 10%
- HLA-matched siblings 20–30%
- Monozygotic twins 70%

NICE Guideline CG86 advise to consider screening if present:

- Addison disease 1.2–12.5%
- Autoimmune liver disease 7%
- Autoimmune myocarditis
- Chronic thrombocytopenic purpura
- Depression or bipolar disorder
- Down syndrome 5–12%
- Epilepsy
- Lymphoma
- Osteoporosis/osteomalacia 1–7%
- Rickets
- Persistent raised liver enzymes without a cause 9%
- Polyneuropathy

- Recurrent miscarriage
- Sarcoidosis
- Sjögren syndrome
- Turner syndrome 6–8%
- Unexplained subfertility

## **Other conditions identified as being associated with increased risk of developing coeliac disease**

- IgA deficiency 7.7%
- Juvenile chronic arthritis 2.5%
- Williams syndrome 8.2-9.5%
- Noonan syndrome

## **Diagnosis**

Diagnosis is based on positive serology, small bowel biopsy with characteristic histology and response to treatment within 2–4 weeks.

### **Serological testing**

IgA TTG (tissue transglutaminase) is currently the first-line investigation of choice for guiding diagnosis. It has very high accuracy with sensitivity between 95 and 97% and specificity between 98 and 100%.

IgA levels are routinely performed in all patients because those with low IgA levels can be falsely negative (IgA deficiency is very common). This group should have IgG to TTG measured because they have a higher incidence of coeliac disease.

### **Small bowel biopsy**

All children with a positive serological test should have small bowel biopsies to confirm the diagnosis before starting a gluten-free diet, although whether children with high TTG levels always need biopsy is the subject of international discussion and debate. Children with high clinical suspicion should be considered for small bowel biopsy even with negative serology because other enteropathies may be found.

The characteristic features on biopsy are of subtotal villous atrophy, crypt hypertrophy, intraepithelial lymphocytosis and a lamina propria plasma-cell infiltrate. These appearances may be patchy and so multiple biopsies are necessary.

## **Differential diagnosis of partial villous atrophy**

- Coeliac disease
- Cows' milk protein sensitive enteropathy
- Soy protein-sensitive enteropathy

- Eosinophilic gastroenteritis
- Gastroenteritis and post-enteritis syndrome
- Giardiasis
- Small bowel bacterial overgrowth
- Inflammatory bowel disease
- Immunodeficiency
- Intractable diarrhoea syndromes, e.g. autoimmune enteropathy
- Drugs, e.g. cytotoxics
- Radiotherapy

## Gluten challenge

There are two common indications for a formal gluten challenge:

1. Patients presenting having restricted or excluded gluten from their diet before the diagnosis being confirmed
2. If the diagnosis of coeliac disease is made at age <2 years and there is any doubt about the full diagnostic criteria being met, a formal gluten challenge should at least be considered.

Gluten challenge involves a period of adequate gluten reintroduction (10–15 g gluten/day), usually at 6 weeks to 3 months, under the supervision of a dietician. Symptomatic relapse may occur rapidly or after many months of gluten exposure and patients should be followed with serial serological testing with biopsy once serology becomes positive.

## Other investigations

HLA-DQ2 or -DQ8 can be considered in specific clinical situations where there is uncertainty in the diagnosis. A negative result indicates that coeliac disease is unlikely.

**Silent coeliac disease** refers to seropositivity with histological evidence of villous atrophy in keeping with a diagnosis of coeliac disease in an asymptomatic individual.

**Latent coeliac disease** refers to seropositivity in the absence of histological changes in the small bowel mucosa to meet the diagnostic criteria for coeliac disease. A significant number of these patients will go on to develop the mucosal changes associated with coeliac disease and its clinical consequences.

**Coeliac crisis** is a rare complication of coeliac disease characterized by explosive diarrhoea, abdominal distension, dehydration and electrolyte disturbance with hypoalbuminaemia, which may necessitate treatment with steroids during the initial phase.

## Management of coeliac disease

A gluten-free diet for life is the only effective treatment for coeliac disease. Children should be seen regularly by a dietician to help with compliance and assess nutritional adequacy. Adherence to a strict gluten-free diet improves growth, normalizes haematological and biochemical markers, and

reduces morbidity. A small proportion of children, who are markedly symptomatic with watery diarrhoea at presentation and do not settle with a gluten-free diet, benefit from a period of lactose exclusion. These patients need monitoring of growth, compliance with gluten-free diet, iron status and other nutritional deficiencies. Iron, calcium and multivitamin supplements are often needed in patients with inadequate intake.

Non-adherence to a gluten-free diet is associated with increased morbidity and mortality as follows:

- Persistent gastrointestinal symptoms, impaired nutrition
- Impaired growth and pubertal development
- Reduced bone mineralization leading to osteoporosis
- Infertility/low-birthweight infants
- Increased risk of gastrointestinal malignancy

If there is problem with compliance, patients need to be seen more regularly by a dietician and a gastroenterology team. It is sometimes necessary to provide support from psychology/mental health team/counsellor/education and social services.

## 9. ABDOMINAL PAIN

Abdominal pain is a very common symptom in childhood. The differential diagnosis varies considerably depending on the presentation. Children who present with acute abdominal pain need urgent evaluation to rule out surgical causes that need intervention, the most common being appendicitis. However, the differential diagnosis is wide and includes many other potential causes. Approach through detailed history, careful physical examination, assessment of pain and associated symptoms. Initial investigations include full blood count, biochemistry, inflammatory markers, serum amylase and urinalysis. Other investigations considered are a chest radiograph if there are chest signs, abdominal radiograph if bowel obstruction is suspected, and abdominal ultrasonography for possible intussusception, pyelonephritis or inflammatory bowel disease.

Differential diagnosis of acute abdominal pain
<ul style="list-style-type: none"><li>• Appendicitis/peritonitis</li><li>• Intussusception</li><li>• Urinary tract infection/pyelonephritis</li><li>• Mesenteric adenitis</li><li>• Constipation</li><li>• Peptic ulceration</li><li>• Meckel diverticulum</li><li>• Pancreatitis</li><li>• Gastroenteritis</li><li>• Inflammatory bowel disease</li><li>• Henoch–Schönlein purpura</li><li>• Hernia/testicular torsion/trauma</li></ul>

- Pelvic inflammatory disease/ovarian pathology
- Cholecystitis
- Sick cell crisis
- Renal colic
- Metabolic, e.g. acute porphyria
- Pneumonia

## 9.1 Recurrent abdominal pain

Recurrent abdominal pain is very common, affecting up to 10% of the school-age population. In most cases the aetiology is non-organic. The condition is more common in girls than in boys and a family history is common. The pain is usually periumbilical and rarely associated with other gastrointestinal symptoms such as diarrhoea, blood per rectum or weight loss. Investigations are usually unhelpful but are considered to rule out underlying organic pathology.

Abdominal pain accompanied by other symptoms suggests organic pathology. Night pain is suggestive of oesophagitis or peptic ulceration. Diarrhoea with blood per rectum suggests a colitis and diarrhoea associated with weight loss suggests a malabsorption syndrome.

Children with chronic abdominal pain lasting for longer than 3 months should have initial investigations including a full blood count, inflammatory markers and coeliac serology, renal function, liver function and urine microscopy with culture.

### Factors that suggest an organic cause

- Age <5 years
- Constitutional symptoms – fever, weight loss, poor growth, joint symptoms, skin rashes
- Vomiting – particularly if bile stained
- Pain that awakens the child from sleep
- Pain away from the umbilicus ± referred to back/shoulders
- Urinary symptoms
- Family history of inflammatory bowel disease, peptic ulcer disease
- Perianal disease
- Occult or gross blood in the stool
- Abnormal screening blood tests

## 9.2 Functional gastrointestinal disorders

Functional gastrointestinal disorders (FGIDs) are defined as a variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. There is a range of disorders affecting children and adolescents. Classification is useful for clinical assessment by subtypes; however, children can often have overlapping symptoms of more than one



subtype.

Cyclical vomiting syndrome	<p>Must include <i>all</i> of the following:</p> <ol style="list-style-type: none"><li>1. Two or more periods of intense nausea and unremitting vomiting or retching lasting hours to days</li><li>2. Return to usual state of health lasting weeks to months</li></ol>
Functional dyspepsia	<p><i>Criteria fulfilled at least once per week for at least 2 months before diagnosis and must include all of the following:</i></p> <ol style="list-style-type: none"><li>1. Persistent or recurrent pain or discomfort centred in the upper abdomen (above the umbilicus)</li><li>2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e. not irritable bowel syndrome)</li><li>3. No evidence of an inflammatory, anatomical, metabolic or neoplastic process that explains the child's symptoms</li></ol>
Irritable bowel syndrome (IBS)	<p><i>Criteria fulfilled at least once per week for at least 2 months before diagnosis and must include all of the following:</i></p> <ol style="list-style-type: none"><li>1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with <i>two or more</i> of the following at least 25% of the time:<ol style="list-style-type: none"><li>(a) improved with defecation</li><li>(b) onset associated with a change in frequency of stool</li><li>(c) onset associated with a change in form (appearance) of stool</li></ol></li><li>2. No evidence of an inflammatory, anatomical, metabolic or neoplastic process that explains the child's symptoms</li></ol>
Abdominal migraine	<p><i>Criteria fulfilled two or more times in the preceding 12 months and must include all of the following:</i></p> <ol style="list-style-type: none"><li>1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more</li><li>2. Intervening periods of usual health lasting weeks to months</li><li>3. The pain interferes with normal activities</li><li>4. The pain is associated with two or more of the following:<ol style="list-style-type: none"><li>(a) anorexia</li><li>(b) nausea</li><li>(c) vomiting</li><li>(d) headache</li><li>(e) photophobia</li><li>(f) pallor</li></ol></li><li>5. No evidence of an inflammatory, anatomical, metabolic or neoplastic process considered that explains the child's symptoms</li></ol>

*Criteria fulfilled at least once per week for at least 2 months before diagnosis and must include all of the following:*

Childhood functional abdominal pain

1. Episodic or continuous abdominal pain
2. Insufficient criteria for other FGIDs
3. No evidence of an inflammatory, anatomical, metabolic or neoplastic process that explains the child's symptoms

---

*Criteria fulfilled at least once per week for at least 2 months before diagnosis:*

Childhood functional abdominal pain syndrome

- Must include childhood functional abdominal pain at least 25% of the time and one or more of the following:
1. Some loss of daily functioning
  2. Additional somatic symptoms such as headache, limb pain and difficulty sleeping

---

From Childhood Functional Gastrointestinal Disorders: Child/Adolescent. *Gastroenterology* 2006;**130**:1527 –37.

## **Associations in children with FGIDs**

### **Personality type**

- Timid, nervous anxious characters, perfectionists, over-achievers
- Increased number of stresses and more likely to internalize problems than other children, but no increase in the risk of depression or other psychiatric problems when compared with children with organic pain
- May be a degree of school refusal or issues in school environment

### **Family factors**

- Marital discord, separation, divorce, excessive arguing
- Extreme parenting – over-submissive or excessive punishment
- History of alcoholism
- Antisocial or conduct disorders, somatization disorders
- High degree of medical complaints in the family members

### **Physical stresses in children**

- Recent physical illness – postviral infection
- Food intolerances – poor diet, intolerance to wheat, carbohydrates
- Multiple medications
- Constipation, lack of exercise, chronic illness

### **Psychosocial stresses in children**

- Death of a family member
- Separation of a family member – divorce, child going to college
- Illness in family member
- Problem in school, altered peer relationship
- Poverty
- Geographical move

## **Clinical approach to recurrent abdominal pain (syndrome)**

### **Positive diagnosis**

Detailed history and examination with initial investigations to rule out organic cause. Rome III criteria often help to classify symptoms into subtypes and guide further investigations. It is important to avoid doing excessive tests, reassure families with normal results and look into possible family factors and stresses.

### **Reassurance and lifestyle changes**

It is important to acknowledge that the pain is real and not psychogenic. Explanation of non-organic nature of the condition with normal initial investigation is useful to gain confidence of child and families. Emphasis should be on rehabilitation. Lifestyle changes help, such as avoiding possible dietary triggers, healthy eating, regular exercise and regular attendance at school; assessment by dietician might be useful. It is important to address associated symptoms such as headaches and constipation. Diary of symptoms useful in severe cases.

### **Pharmacological therapy**

Pharmacological treatments are used, although the evidence base is limited. Avoid excessive use of non-steroidal anti-inflammatory drugs (NSAIDs). H<sub>2</sub>-receptor blockers are useful in functional dyspepsia. Peppermint oil is beneficial in irritable bowel syndrome (IBS). Pizotifen is useful in abdominal migraine. Simple analgesics, antiemetics and antispasmodics are often prescribed although are not generally helpful. Laxatives may be helpful if constipation is present.

### **Psychological intervention**

The aim of psychological treatment is to modify thoughts and behavioural response to symptoms. Acceptance of a biopsychosocial model of the condition by the patient and the family is crucial for the response to treatment. The therapies include biofeedback, relaxation therapy, behavioural and cognitive therapies, coping skills training, family therapy and hypnosis. Graded rehabilitation with a goal-based approach is useful. Patients with severe symptoms need long-term psychological input and follow-up until symptoms resolve.

## **10. INFLAMMATORY BOWEL DISEASE**

Inflammatory bowel disease (IBD) encompasses two related but distinct disorders of as yet unknown aetiology: Crohn disease and ulcerative colitis (UC). ‘Indeterminate colitis’ is a term reserved for

cases of colitis in which findings are not sufficient to allow differentiation between the two and accounts for 10–15% cases. The only prospective national survey (2001) suggested that the incidence of IBD in children under 16 years is 5.2 per 100 000, with Crohn disease being twice as common as ulcerative colitis. Precise aetiology of IBD is unknown and reflects a complex interaction of genetic predisposition, environmental triggers (viral infection, smoking, NSAIDs) and immune dysfunction. IBD runs a chronic relapsing course and the mainstay of the treatment is to maintain growth and nutrition by inducing and maintaining remission with minimal side effects.

## 10.1 Crohn disease

Crohn disease is a chronic idiopathic inflammatory disorder of the bowel involving any region from the mouth to the anus.

The most common presenting symptoms are abdominal pain, diarrhoea and weight loss. Growth failure with delayed bone maturation and delayed sexual development is common. The presentation can be insidious with growth failure as the only presenting feature. Examination might reveal mouth ulcers, pallor and presence of anal tags on perianal examination.

### Investigation

- Full blood count, inflammatory markers (more likely raised in Crohn disease than in UC), and basic biochemistry including liver function tests
- Infective colitis is ruled out by stool culture and checking for *Cl. difficile* toxin
- Endoscopy with biopsies assesses extent of the disease and provides a tissue diagnosis, showing focal lesion with transmural inflammation and granulomas in 40–60% of the cases
- Barium radiology/ultrasonography/MRI (magnetic resonance imaging) to look for small bowel disease
- MRI can be useful in assessment of difficult perianal disease
- In cases with indeterminate histology, immunological markers can be helpful (perinuclear anti-neutrophil cytoplasmic antibody [pANCA] positive in 70% patients with UC and anti-*Saccharomyces cerevisiae* antibody [ASCA] positive in 50–60% patients with Crohn disease)

### Management

The aim of management is to induce and maintain disease remission and thereby facilitate normal growth and development. A multidisciplinary approach is essential including paediatric gastroenterologist, general paediatrician, paediatric surgeon, radiologist, histopathologist, paediatric dietician, nurse specialist and psychologist.

Exclusive enteral nutrition is the most widely used treatment as an exclusion diet for up to 6–8 weeks, followed by a period of controlled food reintroduction. The type of enteral nutrition used varies and can be either elemental (protein broken down into peptide chains or amino acids, e.g. EO28) or polymeric (whole protein, e.g. Modulen IBD). This treatment induces remission in up to 70–80% of

patients. The formula can be flavoured to improve compliance and given by nasogastric tube in cases where it is not tolerated orally.

Corticosteroids are considered in children with severe disease, isolated colitis or failure of response to enteral nutrition. Given as soluble prednisolone or intravenous hydrocortisone and weaned gradually once remission is achieved.

Children often need antacids/proton pump inhibitor if gastritis is present.

Maintaining remission is a challenge as up to 90% of patients relapse in the first 12 months. Maintenance is with 5-aminosalicylic acid (5-ASA) derivatives (poor evidence base), thiopurines, methotrexate and monoclonal antibody therapy. Nutritional requirements are high and long-term continued nutritional support is sometimes needed. Repeated courses of exclusive enteral nutrition or corticosteroids are used for disease flare-ups.

Other supportive treatments: antibiotic courses such as metronidazole for up to 6 weeks can be used in cases of severe perianal disease. Parenteral nutrition may be required in some cases. Oral disease is treated with topical steroids or intralesional steroids.

## **Management of refractory disease**

Refractory Crohn disease is disease unresponsive to first-line treatment including an adequate course of steroid treatment. Second-line treatments for active disease include methotrexate and monoclonal antibody therapy.

### **Immunosuppressive agents**

The most commonly used additional immunosuppressive agents are thiopurines such as azathioprine or 6-mercaptopurine, a metabolite of azathioprine. They reduce steroid requirements (steroid sparing) and will induce a long-term remission in 60–80%. Important toxicity includes the risk of myelosuppression, pancreatitis, hepatitis, rash, flu-like symptoms and infections. Regular blood counts are required for monitoring of bone marrow function. Toxicity is common in patients with low levels of TPMT (thiopurine methyltransferase), an enzyme required for the metabolism of thiopurines.

### **Anti-tumour necrosis factor (TNF) antibodies**

These are indicated for induction of remission in refractory Crohn disease in which surgery is not possible, including cases with fistulating disease. Infliximab is the most widely used, given as an initial course at 0, 2 and 6 weeks, with continued 8-weekly intervals if effective. There is significant potential toxicity and a risk–benefit discussion needs to occur before treatment is started. Patients who become refractory to infliximab can be considered for adalimumab, which is a newer humanized monoclonal antibody effective in Crohn disease.

### **Surgery**

This is considered in isolated ileocaecal disease, stricturing and fistulating disease, and in those with failed medical management. At least 30% will require surgery in the first 10 years of the disease and 70–80% will require surgery in their lifetime.

## 10.2 Ulcerative colitis

Ulcerative colitis is a diffuse (rather than patchy) mucosal inflammation limited to the colonic and rectal mucosa. It is the more distal bowel that is most involved. A backwash ileitis into the terminal ileum is often seen. Aetiology is unknown. Disease is more common in females than males.

### Clinical presentation

The disease can present as distal (proctitis, proctosigmoiditis), left-sided colitis (up to splenic flexure), extensive colitis (up to hepatic flexure) or pancolitis affecting the whole colon (mild, moderate or severe). Pancolitis is the most common presentation in children. Rarely it can present as 'acute toxic colitis'.

The symptoms of colitis are diarrhoea, blood per rectum and abdominal pain. Night stools are common. Systemic disturbance can accompany more severe disease: tachycardia, fever, weight loss, anaemia, hypoalbuminaemia and leukocytosis, and raised inflammatory markers (less common than in Crohn disease).

Although unusual, the disease can present with predominantly extraintestinal manifestations, including growth failure, arthropathy (ankylosing spondylitis – rare in children), erythema nodosum, iritis, uveitis and liver disease (sclerosing cholangitis and autoimmune hepatitis).

Complications of UC include toxic megacolon, growth failure (secondary to prolonged corticosteroids), osteoporosis, cholangitis, increased thrombotic tendency and colon cancer. The cancer risk reflects the disease severity and duration of disease. Regular screening is carried out in adult life. Proximal constipation is common in distal colitis. UC in remission is often associated with development of irritable bowel-type syndrome.

### Diagnosis

- Careful history and examination considering wide differential diagnosis for colitis (see [Section 9.3](#))
- Bloods include full blood count, biochemistry and inflammatory markers (C-reactive protein or CRP and erythrocyte sedimentation rate or ESR) can be normal in some cases
- It is essential to exclude infective colitis by stool culture
- Gastroscopy and colonoscopy give histological diagnosis (mucosal and submucosal inflammation with goblet-cell depletion, cryptitis and crypt abscesses but no granulomas) and helps to assess the severity of the disease. Endoscopy is deferred in severe cases (e.g. toxic megacolon) where empirical treatment is considered
- If liver function is abnormal, more detailed autoantibody screen, liver ultrasonography with consideration of ERCP (endoscopic retrograde cholangiopancreatography)/liver biopsy is indicated

# Management

Treatment depends on disease activity and distribution. Severe disease needs urgent treatment with intravenous steroids.

## Induction of remission

### *Mild or left-sided UC*

Topical mesalazine and steroid treatment is effective with oral 5-ASA derivatives such as mesalazine and sulfasalazine. Oral steroids if 5-ASAs are not effective.

### *Moderate-to-severe UC*

Treat with oral prednisolone for 2–4 weeks at full dose (1–2 mg/kg per day, maximum 40 mg) and weaned gradually over 4–8 weeks.

### *Acute severe colitis/toxic megacolon*

Patient should be admitted to hospital for close monitoring and intravenous steroids. Urgent surgical opinion is needed if toxic megacolon is suspected. Patients not responding to steroids can be considered for ciclosporin or infliximab treatment. Colectomy may be required

## Maintenance of remission

Oral mesalazine or sulfasalazine is the first-line maintenance treatment (monitor liver and renal function 6-monthly). Steroids have no role in maintenance of remission. Azathioprine or 6-mercaptopurine is second line in cases with relapse within 6 months or steroid dependence, with careful monitoring of liver and bone marrow function. 5-ASA derivatives are generally continued long term for the cancer-protective effect.

## Surgery

Can be curative for UC and is required in at least 15% within 5 years of diagnosis and 25% by 10 years. Indications for surgery include failure to respond to medical treatment with morbidity from disease or complications of treatment. Subtotal colectomy and ileostomy are the commonly performed operations with an interval join up (pouch) procedure.

## Differences between Crohn disease and ulcerative colitis

### *Crohn disease*

Panenteric

Skip lesions

Transmural

Granulomas

Perianal disease

### ***Ulcerative colitis***

Colon only

Diffuse

Mucosal

Crypt abscesses

Nutrition is the integral part of management of IBD and nutrition support should be considered where appropriate. Growth needs to be carefully monitored especially in the pubertal years because both the disease and corticosteroid treatment can affect it. Bone health may be poor in IBD and improves with nutritional input, with consideration of vitamin D and calcium supplements when appropriate. Immunosuppressive treatment needs careful monitoring for side effects and immunization advice (no live vaccines while on treatment and varicella immunoglobulin post-exposure if not immune)

## **10.3 Differential diagnosis of colitis**

### **Causes of infective colitis**

- *Salmonella* spp.
- *Shigella* spp.
- *Campylobacter pylori*
- *Escherichia coli* O157 (and other *E. coli*)
- *Clostridium difficile* (pseudomembranous colitis)
- *Yersinia* spp.
- Tuberculosis
- Cytomegalovirus
- *Entamoeba histolytica*

### **Causes of non-infective colitis**

- Ulcerative colitis
- Crohn disease
- Necrotizing enterocolitis
- Microscopic colitis
- Behçet disease
- Eosinophilic enterocolitis

## **10.4 Eosinophilic enterocolitis**

This refers to wide spectrum of involvement of small and large bowel with allergic (eosinophilic) inflammation. Patients may have associated allergies, eczema, asthma or rhinitis. Diagnosis is by presence of gut symptoms, eosinophilic infiltrate (>20 eosinophils per high power field) on biopsies and absence of other causes of eosinophilia (parasitic infection, drugs). Peripheral eosinophilia is not



required for diagnosis but is often present.

- Eosinophilic enterocolitis of infancy is usually dietary protein induced, commonly cows' milk or soya protein. It is a non-IgE-mediated disorder and presents with severe diarrhoea, dehydration, lethargy and acidosis. Treatment is by avoiding the offending antigen and use of amino acid-based formula. Most children outgrow the allergy. The challenge is usually in hospital after 2–3 years with hypersensitivity persisting occasionally
- Eosinophilic proctocolitis of infancy is a milder disorder presenting with blood in the stool in the absence of significant systemic disturbance
- Eosinophilic enterocolitis in older children can affect any part of the bowel and most children have hypersensitivity to foods such as egg, milk, soya and wheat, and a trial of exclusion is attempted. Those not responding to food exclusion may need immunosuppressive treatment including steroids

## 10.5 Pseudomembranous colitis

This occurs secondary to infection with *Clostridium difficile*, which is an increasingly significant pathogen in hospitals. A risk factor is disruption of the normal intestinal flora by antibiotics. Clinical features vary from asymptomatic carriage to life threatening.

Pathogenesis is through toxin production. Treatment is with vancomycin (oral) or metronidazole (intravenous or oral); probiotics may have a role. Relapse rate is 15–20%

## 11. GASTROINTESTINAL BLEEDING

Overt bleeding can happen as a part of an acute illness or as a feature of chronic disease. Obscure bleeding over a long period may present as anaemia. It can be from an upper or lower gastrointestinal source.

### Upper gastrointestinal bleeding

Haematemesis – vomiting frank blood or coffee grounds (soil particles). This needs to be distinguished from haemoptysis.

### Lower gastrointestinal bleeding

- Melaena – offensive black tarry stools
- Haematochezia – bright-red or dark-red blood per rectum

### Obscure gastrointestinal bleeding

Bleeding from a presumed gastrointestinal source when initial investigations such as oesophagogastro-duodenoscopy (OGD) and colonoscopy are normal.

## 11.1 Common causes of gastrointestinal bleeding

Age group	Upper gastrointestinal bleeding	Lower gastrointestinal bleeding
Neonates	Haemorrhagic disease of the newborn Swallowed maternal blood Coagulopathy Stress gastritis Maternal non-steroidal anti-inflammatory drugs Pulmonary haemosiderosis Factitious	Anal fissure/constipation Swallowed maternal blood Malrotation with volvulus Necrotising enterocolitis Maternal idiopathic thrombocytopenic purpura Factitious
Infants (1 month to 1 year)	Mallory–Weiss tear Oesophagitis Gastritis Pulmonary haemosiderosis	Anal fissure Intussusception Gangrenous bowel Milk protein allergy Infective colitis Hirschsprung disease Vascular malformation Factitious
Children	Mallory–Weiss tear Haemorrhagic tonsillitis Peptic ulcer disease Gastritis Oesophageal/gastric varices Pulmonary haemosiderosis Factitious	Anal fissure/constipation Polyps Inflammatory bowel disease Infectious colitis Vascular lesion Meckel diverticulum Haemolytic–uraemic syndrome Henoch–Schönlein purpura Threadworms Factitious
Adolescents	Mallory–Weiss tear Haemorrhagic tonsillitis Oesophagitis/gastritis Peptic ulcer disease Oesophageal/gastric varices Factitious	

- Trace or small amount of upper gastrointestinal (GI) bleeding is not worrying and usually settles down. Children rarely need an extensive work-up and invasive tests and parents can be advised to monitor children at home for a further bleed
- Detailed history and examination with appropriate laboratory tests help with diagnosis. Blood results should be interpreted with caution in cases of acute severe bleeding. Haemoglobin could be falsely high because of haemoconcentration and urea could be high because of absorption of blood from the gut. Bleeding from upper GI can be diagnosed by nasogastric tube lavage and further confirmed by endoscopy. In cases with suspected bleeding from colon (haematochezia), colonoscopy is the initial investigation of choice. If bleeding source is not identified on gastroscopy and colonoscopy or when small bowel bleeding (obscure) is suspected, various radiological investigations are considered such as ultrasonography with Doppler, barium radiology, nuclear radionuclide scan, CT enterography, MR angiography/venography, Meckel diverticulum scan and capsule endoscopy
- Active upper or lower GI bleeding needs resuscitation with assessment of airway, breathing and circulation. In case of circulatory compromise, needs prompt intravenous access followed by fluid resuscitation with possible blood transfusion. These patients should be admitted to a paediatric intensive care unit and need careful monitoring
- Variceal bleeds may need endoscopic control of active haemorrhage with sclerotherapy, an elastic

ligature or (in rare cases) a transjugular intrahepatic portosystemic shunt (TIPS). Failure to control bleeding may require the placement of a Sengstaken–Blakemore balloon for temporary tamponade if endoscopic treatment fails or is not possible at the time due to the massive bleeding. Significant GI bleeding that cannot be controlled may require laparoscopy/laparotomy with intraoperative endoscopy

## 11.2 Intussusception

Peak incidence aged 6–9 months. Male:female ratio 4:1, usually ileocaecal. Presents with spasmodic pain, pallor and irritability. Vomiting is an early feature and rapidly progresses to being bile stained. Passage of blood-stained stools often occurs and a mass is frequently palpable.

Can be secondary to causes such as Meckel diverticulum, polyp, reduplication, lymphosarcoma and Henocho–Schönlein purpura. Diagnosis is clinical and can be confirmed by plain abdominal radiograph, ultrasonography or air–enema examination. Treatment is either with air–enema reduction if the history is short or surgically at laparotomy. Contraindications to air enema include peritonitis and signs of perforation.

## 11.3 Meckel diverticulum

Remnant of the vitellointestinal duct present in 2% of individuals; 50% contain ectopic gastric, pancreatic or colonic tissue. Presents with intermittent, painless blood per rectum; bleeding can be quite severe and may require a blood transfusion; other presentations include intussusception (more common in older boys), perforation and peritonitis. The technetium scan is used to look for ectopic gastric mucosa.

## 11.4 Polyposis

Polyps generally present with painless rectal bleeding or through genetic screening of affected families with polyposis syndromes. Investigation requires upper and lower GI endoscopies with small bowel imaging.

### Classification of polyps

---

	Solitary juvenile polyps – most common
	Juvenile polyposis syndrome
Hamartomas	Peutz–Jeghers syndrome
	Cowden syndrome
	Bannayan–Riley–Ruvalcaba syndrome
	Familial adenomatous polyposis

Adenomas	Gardner syndrome Turcot syndrome
Hyperplastic	Single, antrum/duodenum, benign
Inflammatory	Can be multiple, associated with inflammatory bowel disease, postinfective, ischaemic causes No malignant potential

---

## Juvenile polyps

Account for 85% of the polyps seen in childhood. Present at age 2–6 years with painless blood per rectum. Most polyps are solitary and located within 30 cm of the anus. Not premalignant. Juvenile polyposis syndrome refers to multiple juvenile polyps and can be premalignant.

## Peutz–Jeghers syndrome

Autosomal dominant inheritance. Diffuse GI hamartomatous polyps associated with hyperpigmentation of the buccal mucosa and lips. Premalignant. Polyps generally found in jejunum and can cause bleeding, anaemia, intussusception or obstruction. Endoscopic screening and small bowel imaging start from age 8 years.

## Gardener syndrome and familial adenomatous polyposis coli

Best considered together. Both conditions are inherited as autosomal dominant. Mutation in *APC* (adenomatous polyposis coli) gene located on chromosome 5q21. Gardener syndrome is familial adenomatous polyposis plus bony lesions, subcutaneous tumours and cysts. Both conditions carry a very high risk of colonic carcinoma, and prophylactic colectomy at the end of the second decade is advised. Individuals identified with family specific gene mutations need endoscopic surveillance from their early teens.

## Other polyposis syndromes

- Grolin syndrome – hamartomas, autosomal dominant
- Turcot syndrome – multiple colorectal adenomas with primary brain tumour

## 12. GASTROENTERITIS

Gastroenteritis is a common problem. Most cases can be managed at home. Oral rehydration therapy is the mainstay of treatment, using rapid rehydration over 4–6 hours with reassessment and the early reintroduction of normal feeds after that. Breast-feeding should not be stopped. Antimicrobials are only of use in very specific circumstances. Antidiarrhoeal agents are of no use. Complications such as carbohydrate intolerance and chronic diarrhoea and faltering growth are relatively rare.

The NICE has produced guidelines for diagnosis, assessment and management of acute gastroenteritis in children younger than 5 years (April 2009).

## Composition of oral rehydration solution

Oral rehydration therapy, which has probably saved more children's lives worldwide than any other medical intervention, remains the mainstay of treatment. The World Health Organization's (WHO's) oral hydration solution (ORS) contains 90 mmol/l of sodium and is specifically designed for cholera treatment. European ORS contains between 35 and 60 mmol/l of sodium with varying concentrations of glucose and potassium. There remains controversy over the best combination but it would appear that all of the available formulations are effective and safe. Homemade solutions, usually with an excess of salt, put children at risk of hypernatraemic dehydration.

## Causes of gastroenteritis

- **Unknown** – in both the developed and developing world, no pathogens are identified in up to 50% of cases, even when the condition is fully investigated
- **Viral** – rotaviruses (most common), adenovirus, small-round viruses and astroviruses
- **Bacterial** – *Campylobacter* spp. (most common), *Shigella* spp., *Salmonella* spp., enteropathogenic *E. coli*, enterotoxigenic *E. coli* O157:H7 (rare but associated with haemolytic–uraemic syndrome), *Vibrio cholerae*, *Yersinia enterocolitica*
- **Protozoa** – *Cryptosporidium* sp. (particularly in the immunocompromised host), *Giardia* sp., which has a varied presentation ranging from the asymptomatic carrier state to chronic diarrhoea with growth failure, *Entamoeba histolytica* (amoebic dysentery)

## Differential diagnosis

This is potentially wide and includes many other potential conditions:

- Other infections, e.g. otitis media, tonsillitis, pneumonia, septicaemia, urinary tract infection, meningitis
- Gastro-oesophageal reflux
- Food intolerance
- Haemolytic–uraemic syndrome
- Intussusception
- Pyloric stenosis
- Acute appendicitis
- Drugs, e.g. laxatives, antibiotics

## Assessment of dehydration

### Remember

- Less than 3% of dehydration is clinically not apparent

- A normal capillary refill time ( $<2$  s) makes severe dehydration very unlikely (measured by pressing the skin and measuring the time taken for the skin to re-perfuse)
- Useful signs include reduced skin turgor, dry oral mucosa, sunken eyes and altered consciousness level

Hospital admission should be considered when:

- Diagnosis is unclear/complications have arisen, e.g. carbohydrate intolerance (see [Section 4.4](#))
- Home management fails/unable to tolerate fluids/persistent vomiting
- Severe dehydration
- Significant other medical condition, e.g. diabetes, immunocompromised
- Poor social circumstances
- Hydration difficult to assess, e.g. obesity
- Inability to reassess

## Assessment of dehydration

<i>Percentage dehydration</i>	<i>Severity</i>	<i>Clinical features</i>
3	Undetectable	
3–5	Mild	Slightly dry mucous membranes
5	Moderate	Decreased skin turgor, slightly sunken eyes, depressed fontanelle, circulation preserved
10	Severe	All the above plus more marked drowsiness, rapid weak pulse, cool extremities, capillary refill time $>2$ s
12–14	Moribund	

Children with 10% dehydration usually require intravenous fluid resuscitation.

## 13. CONSTIPATION

Childhood constipation is very common (5–30%). Most children (about 95%) do not have an underlying cause (functional constipation). Delay in treatment can affect physical growth and development, as well as education and psychological wellbeing.

Constipation is ‘delay in passage of stools leading to distress and may include other symptoms such as pain, discomfort, anorexia, soiling, encopresis’.

Soiling is leakage of stools with megarectum. The soiling occurs because the normal sensory process of stool being in the rectum, resulting in distension and the urge to defecate, is lost when the rectum is permanently distended. This should be distinguished from encopresis in which stool is passed into the pants at inappropriate times and in inappropriate places with no underlying constipation – the latter

being a primarily psychological problem:

The definition of chronic constipation (according to the Paris Consensus Group) is the occurrence of two or more of the following characteristics, during the last 8 weeks:

- Frequency of bowel movements <3/week
- More than one episode of faecal incontinence per week
- Large stool in the rectum or palpable on abdominal examination
- Passing of stools so large that they may obstruct the toilet
- Display of retentive posturing and withholding behaviours
- Painful defecation

Many factors can trigger constipation including:

- Intercurrent illness with poor fluid and food intake
- Perianal pathology such as anal fissure or streptococcal infection resulting in stool-withholding cycle
- Difficult early toilet training resulting in stool withholding
- Prolonged faecal impaction leads to megarectum with loss of normal rectal sensation – further stool impaction
- Coexisting functional disorders such as ‘irritable bowel syndrome’

**History and clinical examination** should be aimed at looking for diagnostic clues that indicate functional constipation.

## **Red flags in the history**

- Constipation reported from birth or first few weeks of life
- Failure to pass meconium/delay (more than 48 hours) in a term baby
- Infrequent/very large (ribbon) stools
- Faltering growth
- Previously known or undiagnosed weakness in legs/locomotor delay
- Abdominal distension with vomiting

## **Red flags in the clinical examination**

- Perianal inspection – abnormal appearance/patency/position of anus, anteriorly placed anus or absent anal wink, fissures, fistulae, bruising, tight or patulous anus (think of sexual abuse)
- Gross abdominal distension, palpable faecal mass (in at least half of these patients)
- Spine and gluteal examination – asymmetry of gluteal muscles, scoliosis, evidence of sacral agenesis, overlying skin over sacral region with discoloration, naevi, sinus, hairy patch, lipoma or central pit
- Deformity in lower limbs such as talipes
- Abnormal neuromuscular signs unexplained by any existing condition, such as cerebral palsy
- Abnormal tendon reflexes

# Investigations

In the absence of ‘red flags’ on history and clinical examination, diagnosis is likely to be chronic functional constipation and further investigations are not indicated. The following investigations are sometimes considered:

- Coeliac serology as constipation can be a presenting feature
- Electrolytes (hypercalcaemia), endocrine (hypothyroidism) and micronutrients (iron status looking for iron deficiency anaemia) are checked if suggested by clinical examination
- Abdominal radiograph – selectively used to delineate faecal loading when abdominal examination is difficult or inconclusive. It is also useful if neural tube defect is suspected (vertebral abnormalities)
- Bowel transit studies and anorectal manometry
- Full-thickness rectal biopsy if Hirschsprung disease suspected

# Management of constipation

NICE produced a guideline ‘Constipation in children and young people’ in May 2010.

Most constipation is short term and is readily treated with bulk and/or stimulant laxatives. The management of chronic functional constipation is more difficult and often requires a multidisciplinary approach. It involves drug therapy together with several other principles as described below. Drug therapy alone is rarely effective:

- Explanation of normal bowel function helps understanding of the family and improves compliance. Parents and children should be reassured that constipation is common and responds well to treatment
- High-fibre diet is recommended along with adequate fluid intake because it adds bulk to the stool. Regular exercise promotes peristalsis and helps bowel transit
- Regular toileting is a crucial part of the management. Child should be made to sit on the toilet (with appropriate toilet seat and foot support) on waking, after all meals and before bed. This encourages regular emptying of the rectum
- Behavioural advice and reward schemes (star charts) are helpful to gain child’s trust in the management. Rewards can be given for compliance (sitting on the toilet) at first and then for success (opening bowel in the toilet). Children should not be routinely referred to psychologist or Child and Adolescent Mental Health Services
- Drug treatment: there is very poor evidence base for the drug treatment and practice varies between different units. There are various medications available with different mechanisms of action (see table below) and they need close monitoring and support initially because they can increase soiling and make stools loose, and also to monitor compliance



Class of drug	Example	Mechanism of action
Osmotic laxatives	Lactulose, macrogols, magnesium sulphate, phosphate enema	Draws and retain water in large bowel by osmosis
Stimulant laxatives	Anthraquinones, e.g. senna Bisacodyl, picosulphate	Increase intestinal motility
Lubricants/softeners	Arachis oil, liquid paraffin, docusate	Softens impacted stool
Bulking agents	Fibre, bran, isphagula, methylcellulose	Increase faecal mass and improves peristalsis
Prokinetics	Erythromycin	Improves transit by increasing peristalsis

## Disimpaction

All patients at diagnosis should be considered for disimpaction especially if there is a megarectum. Senna or polyethylene glycol can be used as sole agents in high doses. In severe cases, sodium picosulphate (liquid or sachets) may be required.

Rectal medications (suppositories, enemas) are not used for disimpaction unless all oral medications have failed. Rarely, if oral and rectal treatments fail, manual evacuation of the bowel under anaesthesia is considered.

## Maintenance therapy

Laxatives are often needed for a long period. Treatment needs to be closely monitored along with other supportive strategies, and weaned only after a sustained period of normal stooling with no soiling. Polyethylene glycol (Movicol) is widely used. Senokot given in the evening, at reasonable doses, is effective. Other agents can be used and the choice of agent depends on local preference as well as individual patient circumstances. Children who are toilet training should remain on laxatives until toilet training is well established.

## 13.1 Perianal streptococcal infection

This is a common cause of perianal redness that can present as constipation or perianal pain. Occurs secondary to group A streptococcal infection. Treatment is with penicillin. There may be a need for continuing laxatives.

## Other causes of perianal soreness

- Poor perineal hygiene
- Soiling/encopresis
- Threadworm infestation
- Lactose intolerance (acidic stool)
- Anal fissure
- Sexual abuse (rare)

## 13.2 Hirschsprung disease

Absence of ganglion cells in the myenteric plexus of the most distal bowel. Males more than females; 1 in 5000. Gene on chromosome 10. Associated with Down syndrome; high frequency of other congenital abnormalities. Usually presents in infancy, failure to pass meconium with presentation in the older child being rare – the diagnosis in this group usually being chronic functional constipation. Most children with Hirschsprung disease will never have had a normal bowel habit

- Enterocolitis can occur commonly before or after surgery
- Definitive test is by rectal biopsy to confirm the absence of ganglion cells in the submucosal plexus
- Surgery is excision, usually with temporary colostomy followed by pull-through at a later stage
- Ultra-short-segment Hirschsprung disease is very rare and can present significant diagnostic difficulty

## 14. FURTHER READING

Beattie RM, Dhawan A, Puntis JWL (2009). *Oxford Specialist Handbook of Paediatric Gastroenterology, Hepatology and Nutrition*. Oxford: Oxford University Press.

Benninga M, Candy DC, Catto-Smith AG, *et al.* (2005). The Paris Consensus on Childhood Constipation Terminology (PACCT) Group. *J Paediatr Gastroenterol Nutr* **40**:273–5.

European Society of Paediatric Gastroenterology, Hepatology and Nutrition and the European Society for Clinical Nutrition and Metabolism (2005). Guidelines on Paediatric Parenteral Nutrition of the ESPGHAN and the ESPEN. Supported by the European Society of Paediatric Research (ESPR). *J Paediatr Gastroenterol Nutr* **41**(suppl 2):S1–87.

Gupte GL, Beath SV, Kelly DA (2006). Current issues in the management of intestinal failure. *Arch Dis Child* **91**:259–64.

Rasquin A, Di Lorenzo C, Forbes D, *et al.* (2007). Chronic abdominal pain in children. *BMJ* **334**:997–1002.

Rudolph CD, Vandenplas Y, Di Lorenzo C, *et al.* (2009). Paediatric gastro-oesophageal reflux clinical practice guidelines: joint recommendation of NASPGHAN and ESPGHAN. *J Paediatr Gastroenterol Nutr* **49**:498–547.

Sandhu BK, Fell JME, Beattie RM, Mitton SG (2010). Guidelines for the management of inflammatory bowel disease in children in the United Kingdom. *J Paediatr Gastroenterol Nutr* **50**:S1–13.

Vandenplas Y, Brueton M, Dupont C, *et al.* (2007). Guidelines for the diagnosis and management of cow's milk protein allergy in infants. *Arch Dis Child* **92**:902–8.

Wyllie R, Hyams JS, eds (2011). *Paediatric Gastrointestinal and Liver Disease*, 4th edn. London: Elsevier.

## **NICE guidelines**

*Coeliac disease – Recognition and assessment of coeliac disease*. NICE, February 2010. Available at: [www.nice.org.uk/nicemedia/live/12166/44356/44356.pdf](http://www.nice.org.uk/nicemedia/live/12166/44356/44356.pdf)

*Constipation in children and young people*. NICE, May 2010. Available at: [www.nice.org.uk/nicemedia/live/12993/48741/48741.pdf](http://www.nice.org.uk/nicemedia/live/12993/48741/48741.pdf)

*Crohn's disease – Infliximab and adalimumab TA187*. NICE, May 2010. Available at: <http://guidance.nice.org.uk/TA187/QuickRefGuide/pdf/English>

*Diarrhoea and vomiting in children*. NICE, October 2009. Available at: [www.nice.org.uk/nicemedia/live/11846/47350/47350.pdf](http://www.nice.org.uk/nicemedia/live/11846/47350/47350.pdf)

*Food allergy in children and young people*. NICE, February 2011. Available at: [www.nice.org.uk/nicemedia/live/13348/53214/53214.pdf](http://www.nice.org.uk/nicemedia/live/13348/53214/53214.pdf)

---

# Chapter 11

## Genetics

*Natalie Canham*

---

## CONTENTS

### 1. Chromosomes

- [1.1 Common sex chromosome aneuploidies](#)
- [1.2 Common autosomal chromosome aneuploidies](#)
- [1.3 CGH microarray](#)
- [1.4 MLPA](#)
- [1.5 Qf-PCR](#)
- [1.6 FISH testing](#)
- [1.7 Microdeletion syndromes](#)
- [1.8 Genetic counselling in chromosomal disorders](#)

### 2. Mendelian inheritance

- [2.1 Autosomal dominant \(AD\) conditions](#)
- [2.2 Autosomal recessive \(AR\) conditions](#)
- [2.3 X-linked recessive \(XLR\) conditions](#)
- [2.4 X-linked dominant \(XLD\) conditions](#)
- [2.5 Constructing a pedigree diagram \(family tree\)](#)

### 3. Molecular genetics

- [3.1 DNA \(deoxyribonucleic acid\)](#)
- [3.2 RNA \(ribonucleic acid\)](#)
- [3.3 Polymerase chain reaction \(PCR\)](#)
- [3.4 Reverse transcription PCR \(rt-PCR\)](#)
- [3.5 Next generation sequencing](#)
- [3.6 Exome sequencing](#)

### 4. Trinucleotide repeat disorders

- [4.1 Fragile X syndrome](#)

## **5. Mitochondrial disorders**

## **6. Genomic imprinting**

## **7. Genetic testing**

## **8. Important genetic topics**

[8.1 Ambiguous genitalia](#)

[8.2 Cystic fibrosis](#)

[8.3 Duchenne and Becker muscular dystrophies](#)

[8.4 Neurofibromatosis \(NF\)](#)

[8.5 Tuberous sclerosis](#)

[8.6 Marfan syndrome](#)

[8.7 Homocystinuria](#)

[8.8 Noonan syndrome](#)

[8.9 Achondroplasia](#)

[8.10 Alagille syndrome](#)

[8.11 CHARGE syndrome](#)

[8.12 VATER \(VACTERL\) association](#)

[8.13 Goldenhar syndrome](#)

[8.14 Pierre Robin sequence](#)

[8.15 Potter sequence](#)

## **9. Fetal teratogens**

[9.1 Maternal illness](#)

[9.2 Infectious agents](#)

[9.3 Other teratogens](#)

## **10. Prenatal testing**

## **11. Non-invasive prenatal testing**

## **12. Preimplantation genetic diagnosis (PGD)**

## **13. Genetic counselling**

## **14. Further reading**

---

# Genetics

---

## 1. CHROMOSOMES

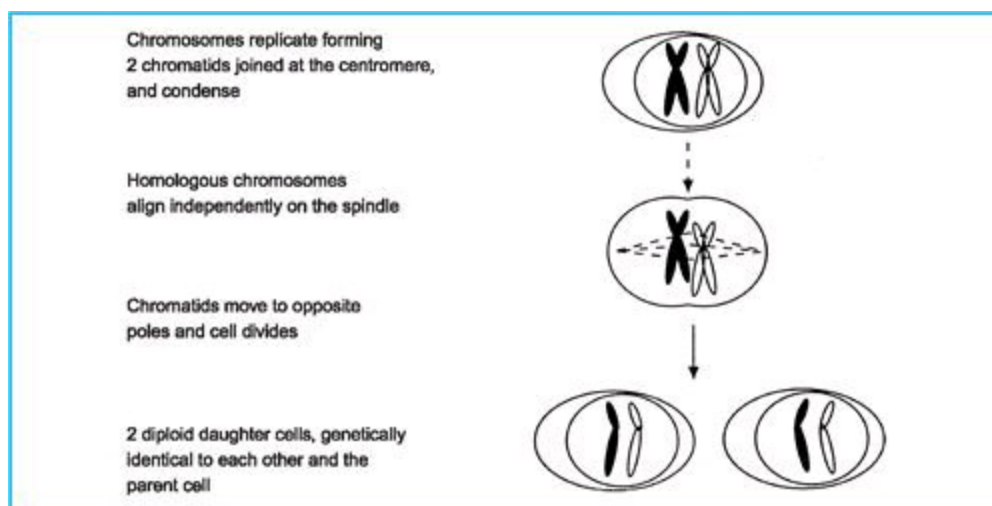
### Background

Within the nucleus of somatic cells there are 22 pairs of autosomes and one pair of sex chromosomes. Normal male and female karyotypes are 46,XY and 46,XX respectively. The normal chromosome complement of 46 chromosomes is known as **diploid**. Genomes with only a single copy of every chromosome or with three copies of each are known respectively as **haploid** and **triploid**. A karyotype with too many or too few chromosomes, where the total is not a multiple of 23, is called **aneuploid**. Three copies of a single chromosome in a cell are referred to as **trisomy**, whereas a single copy is **monosomy**.

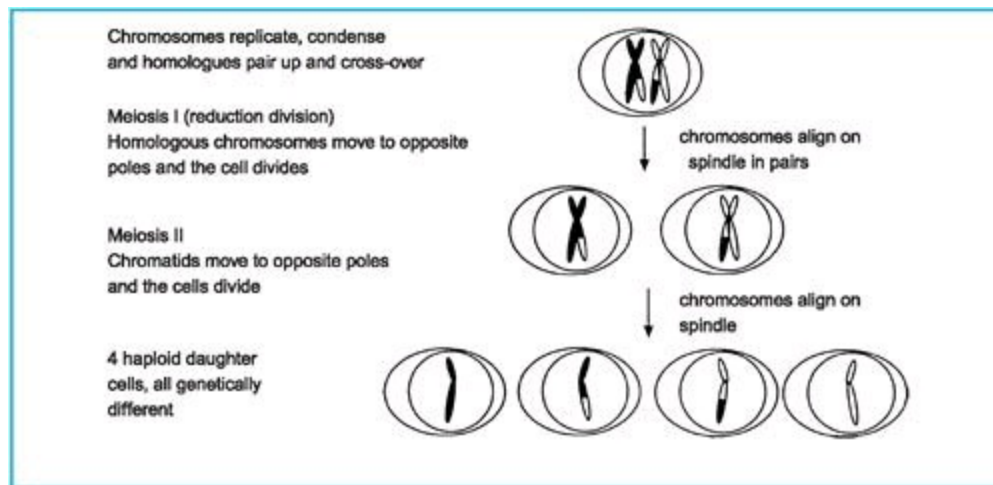
Chromosomes are divided by the centromere into a short 'p' arm ('petit') and a long 'q' arm. **Acrocentric** chromosomes (13, 14, 15, 21, 22) have the centromere at one end and only a q arm.

**Lyonization** is the process in which, in a cell containing more than one X chromosome, only one is active. Selection of the active X chromosome is usually random and each inactivated X chromosome can be seen as a Barr body on microscopy. Genes are expressed only from the active X chromosome.

**Mitosis** occurs in somatic cells and results in two **diploid** daughter cells with nuclear chromosomes which are genetically identical both to each other and the original parent cell.



**Meiosis** occurs in the germ cells of the gonads and is also known as ‘**reduction division**’ because it results in four **haploid** daughter cells, each containing just one member (**homologue**) of each chromosome pair, all genetically different. Meiosis involves two divisions (**meiosis I** and **II**). The reduction in chromosome number occurs during meiosis I and is preceded by exchange of chromosome segments between homologous chromosomes called **crossing over**. In males the onset of meiosis and spermatogenesis is at puberty. In females, replication of the chromosomes and crossing over begins during fetal life but the oocytes remain suspended before the first cell division until just before ovulation.



Meiosis

## Translocations

- **Reciprocal** – exchange of genetic material between non-homologous chromosomes
- **Robertsonian** – fusion of two acrocentric chromosomes at their centromeres, e.g. (14;21)
- **Unbalanced** – if chromosomal material has been lost or gained overall
- **Balanced** – if no chromosomal material has been lost or gained overall

Carriers of balanced translocations are usually phenotypically normal but are at increased risk for having offspring with a chromosomal imbalance. There is also commonly an increased risk of miscarriage and of reduced fertility.

Carriers of a robertsonian translocation involving chromosome 21 are at increased risk of having offspring with translocation Down syndrome. For female and male (14;21) translocation carriers the observed offspring risks for Down syndrome are approximately 15% and 5%, respectively. This may be due to a selective disadvantage to spermatozoa carrying an extra chromosome. Remember, translocation carriers can also have offspring with normal chromosomes or offspring who are balanced translocation carriers like themselves.

### 1.1 Common sex chromosome aneuploidies

## **Turner syndrome (karyotype 45,X)**

This affects 1 in 2500 live-born girls but it is a frequent finding among early miscarriages. Patients are usually of normal intelligence. They have streak ovaries that result in failure of menstruation, low oestrogen with high gonadotrophins and infertility. Normal secondary sexual characteristics may develop spontaneously or can be induced with oestrogens. If puberty is achieved, the uterus is usually normal and pregnancy is possible with the use of donated ova. Short stature throughout childhood with failure of the pubertal growth spurt is typical. Final height can be increased by early treatment with growth hormone. Other features may include:

- Webbed or short neck
- Low hairline
- Shield chest with widely spaced nipples
- Cubitus valgus (wide carrying angle)
- Cardiovascular abnormalities (particularly aortic coarctation in 10–15%)
- Renal anomalies (e.g. horseshoe kidney, duplicated ureters, renal aplasia) in a third
- Non-pitting lymphoedema in a third

## **Triple X syndrome (karyotype 47,XXX)**

This affects 1 in 1000 live-born girls. These patients show little phenotypic abnormality but tend to be of tall stature. Although intelligence is typically reduced compared with siblings it usually falls within normal or low–normal limits. However, mild developmental and behavioural difficulties are more common. Fertility is normal but the incidence of early menopause is increased.

## **Klinefelter syndrome (karyotype 47,XXY)**

This affects 1 in 600 live-born boys. Phenotypic abnormalities are rare prepubertally other than a tendency to tall stature. At puberty, spontaneous expression of secondary sexual characteristics is variable but poor growth of facial and body hair is common. The testes are small and associated with azoospermia, testosterone production is around 50% of normal and gonadotrophins are raised. Gynaecomastia occurs in 30% and there is an increased risk of male breast cancer. Female distribution of fat and hair and a high-pitched voice may occur but are not typical. Intelligence is generally reduced compared with siblings but usually falls within normal or low–normal limits. Mild developmental and behavioural problems are more common.

## **47,XYY males**

This affects 1 in 1000 live-born boys. These males are phenotypically normal but tend to be tall. Intelligence is usually within normal limits but there is an increased incidence of behavioural abnormalities. Previous studies suggesting an increase in criminality have been disproved.

## **1.2 Common autosomal chromosome aneuploidies**



## Down syndrome (trisomy 21)

Down syndrome affects 1 in 700 live births overall and is usually secondary to meiotic non-disjunction during oogenesis, which is more common with increasing maternal age. Around 5% of patients have an underlying robertsonian translocation, most commonly between chromosomes 14 and 21. Around 3% have detectable **mosaicism** (a mixture of trisomy 21 and karyotypically normal cells) usually resulting in a milder phenotype.

Phenotypic features include:

- Brachycephaly
- Upslanting palpebral fissures, epicanthic folds, Brushfield spots on the iris
- Protruding tongue
- Single palmar crease, fifth finger clinodactyly, wide sandal gap between first and second toes
- Hypotonia and moderate learning disability

The following are more common in patients with Down syndrome:

- Cardiovascular malformations in 40%, particularly atrioventricular septal defects
- Gastrointestinal abnormalities in 6%, particularly duodenal atresia and Hirschsprung disease
- Haematological abnormalities, particularly acute lymphoblastic, acute myeloid and transient leukaemias
- Hypothyroidism
- Cataracts in 3%
- Alzheimer disease in the majority by 40 years of age

## Edward syndrome (trisomy 18)

This typically causes intrauterine growth retardation, a characteristic facies, prominent occiput, overlapping fingers (second and fifth overlap third and fourth), rockerbottom feet (vertical talus) and short dorsiflexed great toes. Malformations, particularly congenital heart disease, diaphragmatic hernias, renal abnormalities and dislocated hips, are more common. Survival beyond early infancy is rare but associated with profound learning disability.

## Patau syndrome (trisomy 13)

Affected infants usually have multiple malformations including holoprosencephaly and other central nervous system abnormalities, scalp defects, microphthalmia, mid-line cleft lip and cleft palate, post-axial polydactyly, rockerbottom feet, renal anomalies and congenital heart disease. Survival beyond early infancy is rare and associated with profound learning disability.

## 1.3 CGH microarray

CGH (comparative genomic hybridization) microarray is a method of more detailed chromosome

analysis than that provided by karyotyping. Patient genomic DNA and control genomic DNA are differentially labelled with different fluorescent probes and then hybridized together. The ratio of fluorescent intensity between patient and control DNA is then compared which detects areas of copy number difference. This can detect microdeletions and microduplications as well as anomalies that would have been visible on karyotype. The sensitivity of the test, and thus the size of the imbalances detected, are determined by the distances between and number of the fluorescent probes. High-resolution arrays can detect imbalances as small as 200 base-pairs, but those in current diagnostic use typically detect anomalies above 100 kilobases (kb). Arrays are not able to detect balanced rearrangements, so the karyotype is still appropriate in cases such as recurrent miscarriage. Many small anomalies detected are inherited from a normal parent, and thus are probably not significant in the pathogenesis of developmental problems.

## 1.4 MLPA

MLPA (**m**ultiplex **l**igation-dependent **p**robe **a**mplification) is a multiplex PCR (polymerase chain reaction) method able to detect abnormal copy numbers of multiple genomic DNA sequences. This can be used at a gene level, detecting exon deletions or duplications, or at a chromosomal microdeletion level. Typically kits are generated with a set of probes such as all the telomeres, or the common microdeletion syndromes.

## 1.5 Qf-PCR

Qf-PCR (**q**uantitative **f**luorescence **p**olymerase **c**hain **r**eaction) is a technique allowing fast assessment of copy numbers of whole chromosomes on small samples. Small sections of DNA from the sample are amplified, labelled with fluorescent tags and the amounts measured by electrophoresis. This is most commonly used for identification of aneuploidy on prenatal samples. Typically only chromosomes 13, 18 and 21, and perhaps the sex chromosomes, are tested because no other whole chromosome aneuploidy is survivable to term. Results are available in 24–48 hours.

## 1.6 FISH testing

FISH (**f**luorescent **i**n **s**itu **h**ybridization) is a technique used to assess the copy number of specific DNA sequences in the genome. Fluorescently labelled probes are designed that are complementary to the DNA sequences being assessed, and they are allowed to hybridize to the chromosome spread. The number of copies can then be visualized as fluorescent spots using confocal microscopes. FISH can be performed much more rapidly than formal karyotyping. However, the use of MLPA, Qf-PCR and CGH microarray has largely superseded this process, except in testing other members of a family for a known chromosomal anomaly.

## 1.7 Microdeletion syndromes

These are caused by chromosomal deletions that are too small to see on standard microscopy but involve two or more adjacent (contiguous) genes. They can be detected using specific FISH testing, MLPA or CGH microarray.

Examples of microdeletion syndromes:

- **22q11 microdeletion** (parathyroid gland hypoplasia with hypocalcaemia, thymus hypoplasia with T-lymphocyte deficiency, congenital cardiac malformations, particularly interrupted aortic arch and truncus arteriosus, cleft palate, learning disability) also previously called by many names including DiGeorge syndrome. There appears to be an increased incidence of psychiatric disorders, particularly within the schizophrenic spectrum
- **Williams syndrome** (supravalvular aortic stenosis, hypercalcaemia, stellate irides, characteristic facial appearance, learning disability) due to microdeletions involving the elastin gene on chromosome 7
- **16p11.2 microdeletion syndrome** (autism, seizures, learning disability) no real diagnostic phenotypic features meant that this was not previously identified, but with the widespread use of CGH microarray it is now apparent that this is the most common microdeletion syndrome, found in 1 in every 100 on the autistic spectrum. Frequently also found in a normal parent, giving a high recurrence risk.

## 1.8 Genetic counselling in chromosomal disorders

As a general rule the following apply.

### For parents of a child with trisomy 21

Recurrence risks will be around 1% above the maternal age-related risks for which there are tables. At age 36 years the background risk for Down syndrome is 0.5%. Parents with a robertsonian translocation involving chromosome 21 have a much higher recurrence risk.

### For parents of a child with any other trisomy

Recurrence risks in future pregnancies for that specific trisomy will be <1%. However, couples are generally counselled that there is a 1% risk for any chromosome abnormality in future offspring, which takes into account the small risks that one parent may be mosaic or may have an increased risk of chromosome mis-segregation at meiosis.

### For parents of a child with a microdeletion

Parental chromosomes should be checked. If they are normal, recurrence risks will be <1%. If one parent carries the microdeletion then recurrence risks will be 50%.

### For parents of a child with any other chromosome abnormality

Parental chromosomes should be checked. If they are normal then recurrence risks are usually small (<1%). If one parent carries a predisposing translocation then recurrence risks will be higher, depending on the nature of the translocation.

Prenatal karyotyping is available for any couple who have had a previous child with a chromosome abnormality.

## 2. MENDELIAN INHERITANCE

### 2.1 Autosomal dominant (AD) conditions

These result from mutation of one copy of a pair of genes carried on an autosome. All offspring of an affected person have a 50% chance of inheriting the mutation. Within a family the severity may vary (**variable expression**) and known mutation carriers may appear clinically normal (**reduced penetrance**). Some conditions, such as achondroplasia and neurofibromatosis type 1, frequently start anew through new mutations arising in the egg or (more commonly) sperm.

#### Examples of autosomal dominant conditions

- Achondroplasia
- Alagille syndrome
- Ehlers–Danlos syndrome (most)
- Facioscapulohumeral muscular dystrophy
- Familial adenomatous polyposis
- Familial hypercholesterolaemia
- Gilbert syndrome
- Huntington disease
- Marfan syndrome
- Myotonic dystrophy
- Neurofibromatosis types 1 and 2
- Noonan syndrome
- Porphyrias (except congenital erythropoietic which is AR)
- Tuberous sclerosis
- Von Willebrand disease

Conditions pre-fixed ‘hereditary’ or ‘familial’ are usually autosomal dominant.

### 2.2 Autosomal recessive [AR] conditions

These result from mutations in both copies of an autosomal gene. Where both parents are **carriers** (with only one mutation and a normal copy), each of their offspring has a 1 in 4 (25%) risk of being affected and a 2 in 4 (50%) chance of being a carrier. Carriers are usually indistinguishable from

normal other than by DNA analysis.

## Examples of autosomal recessive conditions

Alkaptonuria  
Ataxia telangiectasia  
 $\beta$ -Thalassaemia  
Congenital adrenal hyperplasias  
Crigler–Najjar syndrome (severe form)  
Cystic fibrosis  
Dubin–Johnson syndrome  
Fanconi anaemia  
Galactosaemia  
Glucose-6-phosphatase deficiency (von Gierke disease)<sup>6</sup>  
Glycogen storage diseases  
Homocystinuria  
Haemochromatosis  
Mucopolysaccharidoses (all except Hunter syndrome)  
Oculocutaneous albinism  
Phenylketonuria  
Rotor (usually)  
Sickle cell anaemia  
Spinal muscular atrophies  
Wilson disease  
Xeroderma pigmentosa

## Risk calculations for AR disorders

Remember:

- People who have no family history of an autosomal recessive disorder have the background population carrier risk
- The parents of a child with an autosomal recessive disorder are assumed to be carriers
- Where both parents are known to be carriers for an autosomal recessive disorder, any of their children who are known to be unaffected are left with a two-thirds carrier risk (because if the possibility that they are affected is discounted, only three possibilities remain).

## Autosomal recessive inheritance and consanguinity

It is believed that everybody carries a few deleterious autosomal recessive genes. First cousins share on average one-eighth of their genes because they share one set of grandparents. As a result, they are more likely to be carrying the same autosomal recessive disorders. For consanguineous couples in a family with a known AR disorder, specific risks should be calculated and appropriate testing should be arranged. For first-cousin parents who have no known family history of any autosomal recessive

disorder, their offspring have around a 3% increased risk above the general background risk of any genetic abnormality of 2% (i.e. a 5% overall risk). Screening should be offered for any autosomal recessive disorder that is available and known to be common in their ancestral ethnic group, e.g.:

- White people – cystic fibrosis
- African/African–Caribbean people – sickle cell anaemia
- Mediterranean/Asian people – thalassaemia
- Jewish people – Tay–Sachs disease and multiple other recessive disorders

Although consanguinity is regarded as taboo in many societies, around 20% of all marriages are consanguineous (second cousin or closer). There are sound financial and societal reasons for consanguineous marriages in societies where these relationships are common, and the majority of offspring are healthy. Geneticists would never advise against consanguineous marriage (or indicate that a child's recessive disorder is the fault of the marriage), but families affected with recessive disorders have been known to employ carrier testing to assist in marriage planning.

## 2.3 X-linked recessive (XLR) conditions

These result from a mutation in a gene carried on the X chromosome and affect males because they have just one gene copy. Females are usually unaffected but may have mild manifestations as a result of lyonization. New mutations are common in many XLR disorders which means that the mother of an affected boy, with no preceding family history, is not necessarily a carrier. XLR inheritance is characterized by the following:

- No male-to-male transmission – an affected father passes his Y chromosome to all his sons
- All daughters of an affected male are carriers – an affected father passes his X chromosome to all his daughters
- Sons of a female carrier have a 50% chance of being affected and daughters have a 50% chance of being carriers

### Examples of X-linked recessive conditions

Alport syndrome (usually XLR; some AR forms)  
Becker muscular dystrophy  
Duchenne muscular dystrophy  
Fabry disease  
Fragile X syndrome  
Glucose-6-phosphate dehydrogenase deficiency (favism)  
Haemophilias A and B (Christmas disease)  
Hunter syndrome (MPS II)  
Lesch–Nyhan disease  
Ocular albinism  
Red–green colour blindness  
Testicular feminization syndrome

## 2.4 X-linked dominant (XLD) conditions

These are caused by a mutation in one copy of a gene on the X chromosome but both male and female mutation carriers are affected. As a result of lyonization, females are usually more mildly affected and these disorders are frequently lethal in males. New mutations are common. For the reasons outlined above:

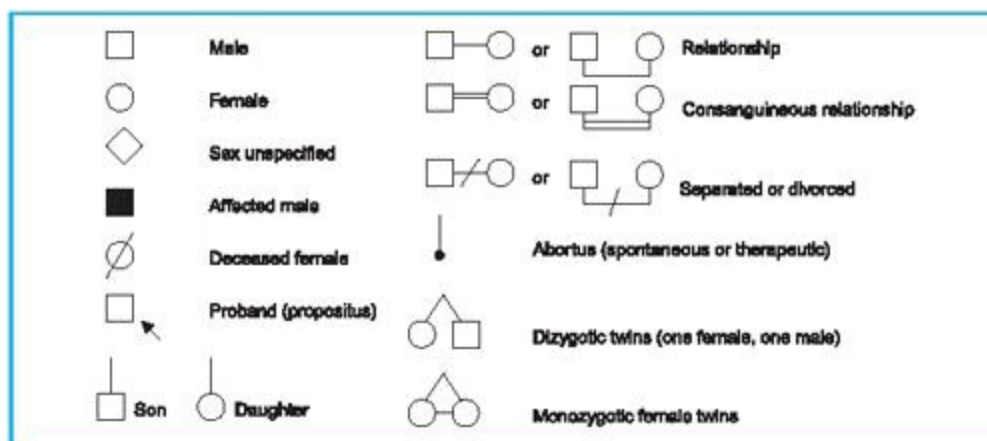
- There is no male-to-male transmission
- All daughters of an affected male would be affected
- All offspring of an affected female have a 50% chance of being affected

### Examples of X-linked dominant conditions include:

Goltz syndrome  
 Incontinentia pigmenti  
 Rett syndrome  
 Hypophosphataemic (vitamin D-resistant) rickets

## 2.5 Constructing a pedigree diagram (family tree)

The basic symbols in common usage are shown in the figure below. Occasionally symbols may be half shaded or quarter shaded. This generally means that the individual manifests a specified phenotypic feature denoted in an accompanying explanatory key, e.g. lens dislocation in a family with Marfan syndrome.



Basic symbols used in pedigree diagrams

## 3. MOLECULAR GENETICS



### 3.1 DNA (deoxyribonucleic acid)

DNA is a **double-stranded** molecule composed of purine (adenine + guanine) and pyrimidine (cytosine and thymine) bases linked by a backbone of covalently bonded **deoxyribose sugar** phosphate residues. The two anti-parallel strands are held together by hydrogen bonds which can be disrupted by heating and reform on cooling:

- **Adenine (A) pairs with thymine (T)** by two hydrogen bonds
- **Guanine (G) pairs with cytosine (C)** by three hydrogen bonds

### 3.2 RNA (ribonucleic acid)

DNA is **transcribed** in the nucleus into messenger RNA (mRNA) which is **translated** by ribosomes in the cytoplasm into a polypeptide chain. RNA differs from DNA in that:

- **It is single-stranded**
- Thymine is replaced by **uracil (U)**
- The sugar backbone is **ribose**

### 3.3 Polymerase chain reaction (PCR)

This is a widely used method for generating large amounts of the DNA of interest from very small samples. PCR can be adapted for use with RNA provided that the RNA is first converted to DNA.

PCR is a method by which a small amount of target DNA (the template) is selectively amplified to produce enough to perform an analysis. This might be the detection of a particular DNA sequence such as that belonging to a pathogenic microorganism or an oncogene, or the detection of differences in genes such as mutations causing inherited disease. Therefore the template DNA might consist of DNA derived from peripheral blood lymphocytes, a tumour biopsy or a biological fluid from a patient with an infection.

In order to perform PCR, the sequence flanking the target DNA must usually be known so that specific complementary oligonucleotide sequences, known as primers, can be designed. The two unique primers are then mixed together with the DNA template, deoxyribonucleotides (dATP, dCTP, dGTP, dTTP) and a thermostable DNA polymerase (Taq polymerase, derived from an organism that inhabits thermal springs):

- In the initial stage of the reaction the DNA template is heated (typically for about 30 seconds) to make it single stranded. As the reaction cools the primers will anneal to the template if the appropriate sequence is present.
- The reaction is then heated to 72°C (for about a minute) during which time the Taq DNA polymerase synthesises new DNA between the two primer sequences, doubling the copy number of the target sequence.

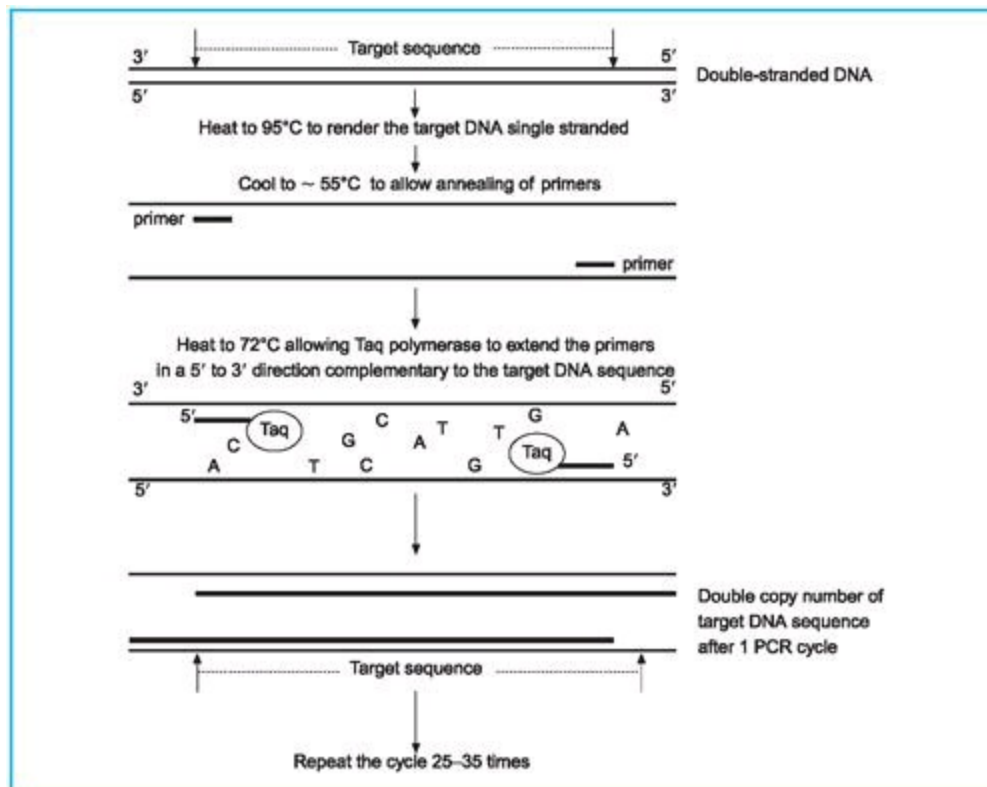


- The reaction is heated again and the cycle is repeated. After 30 or so cycles (each typically lasting a few minutes) the target sequence will have been amplified exponentially.

The crucial feature of PCR is that to detect a given sequence of DNA it only needs to be present in one copy (i.e. one molecule of DNA): this makes it extremely powerful.

## Clinical applications of PCR

- Mutation detection
- Single cell PCR of in vitro fertilized embryo to diagnose genetic disease before implantation
- Detection of viral and bacterial sequences in tissue (herpes simplex virus in CSF, hepatitis C, HIV in peripheral blood, meningococcal strains)



Polymerase chain reaction

## 3.4 Reverse transcription PCT (rt-PCR)

This is a modification of conventional PCR used to amplify messenger RNA (mRNA) sequence in order to look at the expression of particular genes within a tissue. mRNA is single stranded, unstable and not a substrate for Taq DNA polymerase. For that reason it must be converted to complementary DNA (cDNA) using reverse transcriptase, a retroviral enzyme, which results in a double-stranded DNA copy of the original RNA sequence. PCR can then be performed in the normal way.

## 3.5 Next generation sequencing

DNA sequencing is used to identify point mutations, or small deletions/duplications, in a specific gene. Typically a small number of individuals' DNA is tested for mutations in one gene. This is expensive in terms of time and substrates. Next generation sequencing allows multiple parallel analyses to be performed at the same time. This can be used to test a single individual's DNA for mutations in multiple genes, or to test large numbers of individuals at the same time. Chips are being developed for specific related conditions caused by multiple genes, such as aortic dissection, Noonan syndrome, cardiomyopathies and cardiac arrhythmias. These will allow rapid genetic diagnosis of individuals with a clinical diagnosis. Next generation technology is also the basis of exome sequencing.

### 3.6 Exome sequencing

Whole genome sequencing is expensive and time-consuming. The exome consists of only the coding sequences in the genome, i.e. the parts of the genome that are translated into protein. This only represents around 5% of the total genome, but is estimated to contain 85% of all disease-causing mutations. Exome sequencing is a method of analysing the entire exome for mutations. This is primarily a research tool used to identify unknown genes responsible for mendelian disorders, but has also been used to identify functional variation associated with more common conditions such as Alzheimer disease.

## 4. TRINUCLEOTIDE REPEAT DISORDERS

These conditions are associated with genes containing stretches of repeating units of three nucleotides and include:

- Fragile X syndrome – X-linked
- Myotonic dystrophy – AD
- Huntington disease – AD
- Friedreich ataxia – AR
- Spinocerebellar ataxias – AD

In normal individuals the number of repeats varies slightly but remains below a defined threshold. Affected patients have an increased number of repeats, called an **expansion**, above the disease-causing threshold. The expansions may be unstable and enlarge further in successive generations causing increased disease severity ('**anticipation**') and earlier onset, e.g. **myotonic dystrophy**, particularly congenital myotonic dystrophy after transmission by an affected mother. Between the normal range and the affected range, there are two other expansion sizes. **Premutation** sizes are smaller than the lowest copy number to cause disease and are not associated with a risk of the condition, but have a high risk of increasing into the disease range during gametogenesis, generating an affected child. This risk can be gender dependent in some conditions. **Intermediate alleles** are smaller than the premutation range, but larger than normal. They have a risk of increasing into the premutation range during gametogenesis.

## 4.1 Fragile X syndrome

This causes learning disability, macro-orchidism, autism and seizures, and was historically associated with a cytogenetically visible constriction (‘fragile site’) on the X chromosome. The inheritance is X linked but complex. Among controls there are between 6 and 45 stably inherited trinucleotide repeats in the *FMRI* gene. The intermediate allele size is 50–58 repeats, and people with between 58 and 230 repeats are premutation carriers but are unaffected. Only female gametogenesis carries a risk of expansion into the disease-causing range (230 to >1000 repeats) known as a full mutation which is methylated, effectively inactivating the gene. All males and around 50% of females with the full mutation are affected, though females are typically less severely affected. The premutation does not expand to a full mutation when passed on by a male. Male premutation carriers are known as normal transmitting males and will pass the premutation to all their daughters (remember that they pass their Y chromosome to all their sons). Although premutation carrier status is not associated with learning disability, female carriers have a high risk (around 50%) of premature ovarian failure or early menopause. There is also a condition called **fragile X-associated tremor and ataxia syndrome (FXTAS)**, which predominantly affects male premutation carriers over the age of 50. Parkinsonism and cognitive decline are also features. The lifetime male risk of developing FXTAS is 30–40% though 75% of men older than 80 show signs.

## 5. MITOCHONDRIAL DISORDERS

Mitochondria are **exclusively maternally inherited**, deriving from those present in the cytoplasm of the ovum. They contain copies of their own **circular 16.5-kilobase chromosome** carrying genes for several respiratory chain enzyme subunits and transfer RNAs. Mitochondrial genes differ from nuclear genes in having no introns and using some different amino acid codons. Within a tissue or even a cell there may be a mixed population of normal and abnormal mitochondria known as **heteroplasmy**. Different proportions of abnormal mitochondria may be required to cause disease in different tissues, known as a **threshold effect**. Disorders caused by mitochondrial gene mutations include:

- **MELAS** (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes)
- **MERRF** (myoclonic epilepsy, ragged red fibres)
- Mitochondrially inherited diabetes mellitus and deafness (typically caused by the same mutation as seen in MELAS but at lower levels)
- Leber hereditary optic neuropathy (note that other factors also contribute)

Prader-Willi syndrome		Angelman syndrome
Clinical		

Neonatal hypotonia and poor feeding	Unprovoked laughter/clapping
Moderate learning disability	Microcephaly, severe learning disability
Hyperphagia + obesity in later childhood	Ataxia, broad-based gait
Small genitalia	Seizures, characteristic EEG
<b>Genetics</b>	
70% deletion on paternal chromosome 15	80% deletion on maternal chromosome 15
30% maternal uniparental disomy 15	2–3% paternal uniparental disomy 15
(i.e. no maternal contribution)	(i.e. no paternal contribution) remainder due to subtle mutations

## 6. GENOMIC IMPRINTING

For most genes both copies are expressed but for some genes, either the maternally or paternally derived copy is preferentially used, a phenomenon known as genomic imprinting. The unused copy is frequently methylated, which inactivates the gene. These genes tend to aggregate together in **imprinted regions** on chromosomes. Abnormalities of inheritance or methylation of imprinted genes can therefore cause disease even in the presence of two apparently normal copies. The best examples are the Prader–Willi and Angelman syndromes, both caused by cytogenetic deletions of the same region of chromosome 15q, **uniparental disomy** of chromosome 15 (where both copies of chromosome 15 are derived from one parent with no copy of chromosome 15 from the other parent), or abnormalities of methylation, which labels both chromosomes as deriving from one parent. The disease condition is caused by the absence of one parent's copy of genes in the region, rather than by excessive numbers of copies of the other.

### Other imprinting disorders

#### Silver–Russell syndrome

Prenatal onset growth retardation, relative macrocephaly, triangular facies, asymmetry, fifth finger clinodactyly and frequently normal IQ. Around 35% are caused by abnormal methylation of genes on chromosome 11p15, whereas 10% are associated with maternal uniparental disomy of chromosome 7. The cause in the remainder is not yet known.

#### Beckwith–Wiedemann syndrome

Prenatal-onset macrosomia, facial naevus flammeus, macroglossia, ear lobe creases, pits on the ear helix, hemihypertrophy, nephromegaly, exomphalos (omphalocele) and neonatal hypoglycaemia. There is an increased risk of Wilms tumour, adrenocortical and hepatic tumours in childhood. Similar to Silver–Russell syndrome, the condition results from abnormalities of inheritance or methylation of chromosome 11p15 which contains several imprinted genes, including the *IGF-2* (insulin-like growth factor 2) gene. The results in BWS tend to be directly opposite to those in Silver–Russell syndrome.

## 7. GENETIC TESTING

Genetic tests can be thought of as diagnostic, predictive or for carrier status. Informed verbal, and increasingly written, consent (or assent) should be obtained before genetic testing.

### Diagnostic tests

These are chromosomal investigations such as karyotype and CGH microarray, or mutation analysis of specific genes. The latter is frequently used where the diagnosis is already suspected on clinical grounds but genetic testing is useful for confirmation, or for counselling or predictive testing in the wider family.

### Predictive tests

When an individual is clinically normal but is at risk for developing a familial disorder, such as Huntington disease, myotonic dystrophy or a familial cancer syndrome. Predictive testing is not usually offered without a formal process of genetic counselling over more than one consultation with time built in for reflection. Where there are intervening relatives whose genetic status may be indirectly revealed, there are additional issues that must be taken into consideration. Written consent for predictive testing is required by most laboratories. Nationally agreed guidance is that predictive testing in children for disorders that have no implications in childhood should not be undertaken until the child is old enough to make an informed choice.

### Carrier tests

These are usually undertaken in autosomal recessive or X-linked recessive disorders where the result has no direct implications for the health of the individual, but is helpful in determining the risks to their offspring. Carrier status may be generated as a by-product of diagnostic or prenatal testing. National guidance is that specific testing for carrier status should be avoided in children until they are old enough to make an informed choice.

### Genetics in children

Diagnostic tests are obviously necessary and useful, as are predictive tests for disorders that may manifest in childhood, and have a screening programme or treatment, such as the multiple endocrine neoplasias (MEN1, MEN2) and familial adenomatous polyposis. Predictive testing for adult onset disorders such as *BRCA-1/-2* or Huntington disease are not appropriate in children, because they are unable to give informed consent, and a diagnosis can never be removed once it has been made. Many adults opt not to have predictive tests for untreatable disorders such as Huntington disease, and an at-risk child should be allowed to make the same decision. Equally, carrier status for AR or X-linked disorders will impact only on a child's reproductive decisions, not childhood health, and thus is only tested when the child is able to participate in the process and give proper informed consent. Parents do occasionally request such testing, and a clinical geneticist would meet them in clinic to discuss

their reasons for testing and the reasons for a reluctance to offer it.

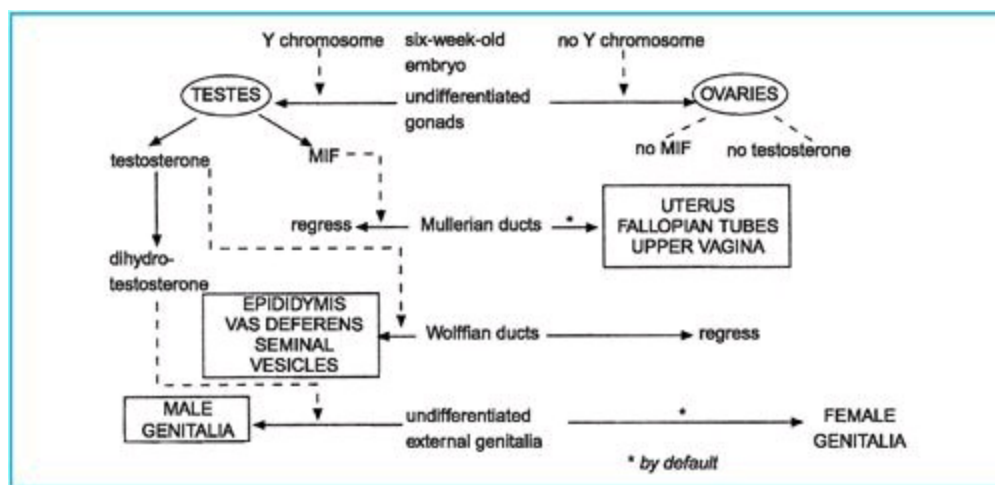
## 8. IMPORTANT GENETIC TOPICS

This section includes short notes on conditions that form popular examination topics.

### 8.1 Ambiguous genitalia

#### Normal development of the reproductive tract and external genitalia

A simplified outline is shown below.



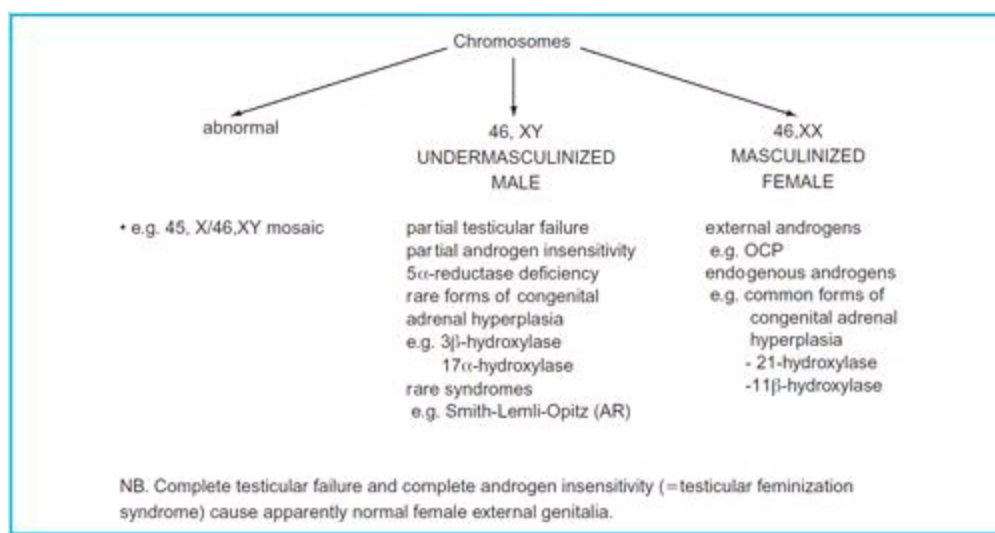
Outline of the normal development of the reproductive tract and external genitalia

The 6-week embryo has undifferentiated gonads, müllerian ducts (capable of developing into the uterus, fallopian tubes and upper vagina), wolffian ducts (capable of forming the epididymis, vas deferens and seminal vesicles) and undifferentiated external genitalia.

In the presence of a Y chromosome the gonads become testes that produce testosterone and müllerian inhibiting factor (MIF). Testosterone causes the wolffian ducts to persist and differentiate and, after conversion to dihydrotestosterone (by  $5\alpha$ -reductase), masculinization of the external genitalia. MIF causes the müllerian ducts to regress.

In the absence of a Y chromosome the gonads become ovaries which secrete neither testosterone nor MIF and, in the absence of testosterone, the wolffian ducts regress and the external genitalia feminize. In the absence of MIF, the müllerian ducts persist and differentiate.

The causes of **ambiguous genitalia** divide broadly into those resulting in undermasculinization of a male fetus, those causing masculinization of a female fetus, and those resulting from mosaicism for a cell line containing a Y chromosome and another that does not. They are summarized in the diagram opposite.



Ambiguous genitalia – outline of causes

## 8.2 Cystic fibrosis

This results from mutations in the *CFTR* (cystic fibrosis transmembrane regulator) gene. The  $\Delta F508$  mutation (deletion of three nucleotides coding for a phenylalanine residue at amino acid position 508) accounts for 75% of mutations in white people. Most laboratories now screen for 32 common mutations including  $\Delta F508$ . Such testing identifies 90% of cystic fibrosis mutations in white people, but a much smaller proportion in many other ethnic groups. Therefore, negative molecular testing cannot exclude a diagnosis of cystic fibrosis.

## 8.3 Duchenne and Becker muscular dystrophies

These result from different mutations within the dystrophin gene on chromosome Xp21.

Important distinguishing features of Duchenne and Becker muscular dystrophies		
	Duchenne muscular dystrophy	Becker muscular dystrophy
Immunofluorescent dystrophin on muscle biopsy	Undetectable	Reduced/abnormal
Wheelchair dependence	95% at <12 years	5% at <12 years
Learning disability	20%	Rare

In around a third of boys with Duchenne muscular dystrophy, the condition has arisen as a new mutation, whereas a further third are the result of a new mutation in the mother. Mutation analysis in



the affected boy can often identify mothers who are carriers, but a normal result does not exclude germline mosaicism, where mutated cells are present in the ovaries but not the blood. A woman proven to be a carrier has a 25% (1 in 4) recurrence risk, but a woman without the mutation in her blood still has up to a 20% recurrence risk, and prenatal diagnosis is offered in all circumstances.

Given the high new mutation rate, both in the affected child and in the mother, calculation of risks to other family members can be challenging. The risk that the mother of an isolated case is a carrier is two in three. The maternal grandmother's risk is one in three, due to the chance of a new mutation in the mother. Thus, the sister of the isolated affected boy has a one in three risk of being a carrier, but the maternal aunt has a one in six risk, and so on.

In practical terms, most families will have an identifiable mutation, and thus carrier identification will be relatively easy. In the absence of a mutation, e.g. the affected individual has died with no DNA stored, or no mutation is identified (a small proportion), then the above risks can be modified using linkage to the X chromosome and Bayes theorem to take into account the number of unaffected males in the family, and the creatine kinase (CK) levels in the at-risk females. Carrier females can have elevated CK levels, although a normal result does not exclude carrier status because they follow a normal distribution. A woman known to be at high risk, but with no identifiable mutation, may only be able to opt to terminate male pregnancies if she wishes to avoid having an affected child.

## 8.4 Neurofibromatosis

There are two forms of neurofibromatosis (NF) that are clinically and genetically distinct:

	NF1	NF2
<b>Major features</b>	<ul style="list-style-type: none"> <li>≥6 Café-au-lait patches</li> <li>Axillary/inguinal freckling</li> <li>Lisch nodules on the iris</li> <li>Peripheral neurofibromas</li> </ul>	<ul style="list-style-type: none"> <li>Bilateral acoustic neuromas (vestibular schwannomas)</li> <li>Other cranial and spinal tumours</li> </ul>
<b>Minor features</b>	<ul style="list-style-type: none"> <li>Macrocephaly</li> <li>Short stature</li> </ul>	<ul style="list-style-type: none"> <li>Café-au-lait patches (usually &lt;6)</li> <li>Peripheral schwannomas</li> <li>Peripheral neurofibromas</li> </ul>
<b>Complications</b>	<ul style="list-style-type: none"> <li>Plexiform neuromas</li> <li>Optic glioma (2%)</li> <li>Other cranial and spinal tumours</li> <li>Pseudarthrosis (especially tibial)</li> <li>Renal artery stenosis</li> <li>Phaeochromocytoma</li> <li>Learning difficulties</li> <li>Scoliosis</li> <li>Spinal cord and nerve compressions</li> <li>Malignant change/sarcomas</li> </ul>	<ul style="list-style-type: none"> <li>Deafness/tinnitus/vertigo</li> <li>Lens opacities/cataracts</li> <li>Spinal cord and nerve compressions</li> <li>Malignant change/sarcomas</li> </ul>



<b>Gene</b>	Chromosome 17	Chromosome 22
<b>Protein</b>	Neurofibromin	Schwannomin

## 8.5 Tuberous sclerosis

There are at least two separate genes that cause tuberous sclerosis (TS), on chromosomes 9 (*TSC1*; hamartin) and 16 (*TSC2*; tuberin).

Clinical features of tuberous sclerosis
<div>Skin/nails</div> <ul style="list-style-type: none"> <li>Ash-leaf macules</li> <li>Shagreen patches (especially over the lumbosacral area)</li> <li>Adenoma sebaceum (facial area)</li> <li>Subungual/periungual fibromas</li> </ul>
<div>Eyes</div> <ul style="list-style-type: none"> <li>Retinal hamartomas</li> </ul>
<div>Heart</div> <ul style="list-style-type: none"> <li>Cardiac rhabdomyomas, detectable antenatally, usually regressing during childhood</li> </ul>
<div>Kidneys</div> <ul style="list-style-type: none"> <li>Angiomyolipomas</li> <li>Renal cysts</li> </ul>
<div>Neurological</div> <ul style="list-style-type: none"> <li>Seizures</li> <li>Learning disability</li> </ul>
<div>Neuroimaging</div> <ul style="list-style-type: none"> <li>Intracranial calcification (periventricular)</li> <li>Subependymal nodules</li> <li>Neuronal migration defects</li> </ul>

## 8.6 Marfan syndrome

This results from mutations in the fibrillin 1 (*FBNI*) gene on chromosome 15. Intelligence is usually normal. New diagnostic criteria do not include joint laxity or hyperextensibility, and this alone in a tall individual is not sufficient to suspect the diagnosis of Marfan.

### Clinical features of Marfan syndrome

#### Musculoskeletal

- Tall stature with disproportionately long limbs (dolichostenomelia)
- Characteristic facial appearance
- Arachnodactyly
- Pectus carinatum or excavatum
- Scoliosis
- High, narrow arched palate with dental overcrowding
- Pes planus

#### Heart

- Aortic root dilatation and dissection
- Mitral valve prolapse

#### Eyes

- Lens dislocation (typically up)
- Myopia

#### Skin

- Striae

#### Lungs

- Spontaneous pneumothorax
- Apical bullae

## 8.7 Homocystinuria

(see also Chapter 16)

This is most commonly the result of cystathione- $\beta$ -synthase deficiency and causes a Marfan

syndrome-like body habitus, lens dislocation (usually down), learning disability, thrombotic tendency and osteoporosis. Treatment includes a low methionine diet  $\pm$  pyridoxine.

## 8.8 Noonan syndrome

This is an autosomal dominant condition. Around 50% of individuals with Noonan syndrome have mutations in the *PTPN11* (protein-tyrosine phosphatase, non-receptor-type 11) gene on chromosome 12. A further 10–15% are caused by *SOS1* (son of seven-less homologue 1 (*Drosophila*), on chromosome 2) and *RAF1* (v-raf-1 murine leukaemia viral oncogene homologue 1 on chromosome 3) causes another 5–10%. Multiple other genes on the RAS-MAPK pathway have also been implicated in small proportions of cases. The karyotype is usually normal.

### Clinical features of Noonan syndrome

#### Cardiac

- Pulmonary valve stenosis
- Hypertrophic cardiomyopathy
- Septal defects (atrial and ventricular septal defects)
- Branch pulmonary artery stenosis

#### Musculoskeletal

- Webbed or short neck
- Pectus excavatum or carinatum
- Wide-spaced nipples
- Wide carrying angle (cubitus valgus)
- Short stature in 80%

#### Other features

- Ptosis
- Low-set and/or posteriorly rotated ears
- Small genitalia and undescended testes in boys
- Coagulation defects in 30% (partial factor XI:C, XIIC and VIIC deficiencies, von Willebrand disease, thrombocytopenia)
- Mild learning disability in 30%

## 8.9 Achondroplasia

A short-limb skeletal dysplasia resulting from specific autosomal dominant mutations in the *FGFR3* (fibroblast growth factor receptor 3) gene on chromosome 4. There is a high new mutation rate.

Important complications are hydrocephalus, brain-stem or cervical cord compression resulting from a small foramen magnum, spinal canal stenosis, kyphosis and sleep apnoea. Intelligence is usually normal.

## 8.10 Alagille syndrome

A variable autosomal dominant disorder resulting from deletions of or mutations in the *JAG1* (jagged) gene on chromosome 20. Major features of the syndrome include:

- Cardiac – peripheral pulmonary artery stenosis ± complex malformations
- Eye – posterior embryotoxon, abnormalities of the anterior chamber
- Vertebral – butterfly vertebrae, hemivertebrae, rib anomalies
- Hepatic – cholestatic jaundice, paucity of intrahepatic bile ducts

## 8.11 CHARGE syndrome

A malformation syndrome including:

- Colobomas
- Heart malformations
- Atresia of the choanae
- Retardation of growth and development (learning disability)
- Genital hypoplasia (in males)
- Ear abnormalities (abnormalities of the ear pinna, deafness)
- Cleft lip/palate and renal abnormalities are also common

The majority of patients with CHARGE syndrome have new mutations or deletions of the *CHD7* (chromodomain helicase DNA-binding protein 7) gene on chromosome 8.

## 8.12 VATER (VACTERL) association

A sporadic malformation syndrome including:

- Vertebral abnormalities
- Anal atresia ± fistula
- Cardiac malformations
- Tracheo-oesophageal fistula
- Renal anomalies, radial ray defects
- Limb anomalies, especially radial ray defects

The cause is not yet known.

## 8.13 Goldenhar syndrome

Also known as oculo-auriculovertebral spectrum, or first and second and branchial arch syndrome. It is mainly sporadic and the cause is unknown. Major features include:

- Craniofacial – asymmetry, hemifacial microsomia, micrognathia
- Ears – malformed pinnae, deafness, preauricular tags
- Eyes – epibulbar (scleral) dermoid cysts, microphthalmia
- Oral – macrostomia, cleft lip/palate
- Vertebral – hemivertebrae
- Cardiac – cardiac malformations
- Renal – renal malformations

## 8.14 Pierre Robin sequence

An association of micrognathia and cleft palate which may occur alone, but a proportion will have 22q11 deletions or Stickler syndrome.

## 8.15 Potter sequence

Oligohydramnios as a result of renal abnormalities, urinary tract obstruction or amniotic fluid leakage may lead to secondary fetal compression with joint contractures (arthrogryposis), pulmonary hypoplasia and squashed facies known as the Potter sequence.

# 9. FETAL TERATOGENS

## 9.1 Maternal illness

### Maternal diabetes

Maternal diabetes is associated with fetal macrosomia, neonatal hypoglycaemia and increased risk of a wide variety of malformations, particularly cardiac (transposition of the great arteries, aortic coarctation, septal defects, cardiomyopathy), vertebral (sacral abnormalities, hemivertebrae), renal (agenesis, duplex collecting systems), intestinal (imperforate anus, other atresias) and limb abnormalities (short femurs, radial ray abnormalities).

### Maternal myasthenia gravis

This is associated with fetal arthrogryposis.

## **Maternal phenylketonuria**

Although the fetus is unlikely to be affected by phenylketonuria (PKU: which is autosomal recessive), if an affected mother has relaxed her low phenylalanine diet, the fetus is at risk of microcephaly, cardiac defects and learning disability secondary to exposure to the raised maternal phenylalanine levels.

## **Maternal systemic lupus erythematosus**

Maternal systemic lupus erythematosus (SLE) with anti-Ro and anti-La antibodies is associated with an increased risk of fetal bradycardia and congenital heart block for which pacing may be required. A self-limiting neonatal cutaneous lupus may also occur.

## **9.2 Infectious agents**

The following agents are associated with increased fetal loss in the first trimester; hepatosplenomegaly, jaundice and thrombocytopenia in the neonate; and abnormalities particularly those affecting the central nervous system, vision and hearing.

### **Fetal cytomegalovirus**

Infection may be associated with microcephaly, intracranial calcification, chorioretinopathy, deafness and learning disability.

### **Fetal toxoplasmosis**

Infection with *Toxoplasma* species, a protozoan, may be associated with microcephaly, hydrocephalus, intracranial calcification, chorioretinopathy and learning disability.

### **Fetal rubella**

Infection with rubella virus is most often associated with deafness particularly in the first and early second trimesters, but cardiac abnormalities (persistent ductus arteriosus, peripheral pulmonary stenosis, septal defects), microcephaly, chorioretinopathy, cataract and learning disability are also associated.

### **Congenital syphilis, herpes and varicella**

See Chapter 15, Section 11.1.

## **9.3 Other teratogens**

## **Fetal alcohol syndrome**

Pre- and postnatal growth retardation, neonatal irritability, microcephaly, learning disability, hyperactivity in childhood, cardiac defects (particularly ventricular and atrial septal defects), small nails on fifth fingers and toes, facial anomalies (short palpebral fissures, ptosis, smooth philtrum, thin upper lip) and a variety of less common, often midline, malformations. It is likely that the effects on any one fetus are determined by the degree, timing and duration of exposure as well as the susceptibility of the fetus which is probably genetically determined.

## **Illicit drugs in pregnancy**

Opiate drugs in pregnancy have a high risk of dependency in the newborn, intrauterine growth retardation and still birth, but do not appear to be associated with significant risk of structural anomalies. There are behavioural issues during childhood. Fetal cocaine has a higher risk of defects, apparently associated with vascular disruption, such as limb reduction defects and porencephaly. Survivors of this do not appear to have long-term intellectual deficit once their home circumstance has been taken into account, though there is evidence of some attention and behavioural problems.

## **Fetal retinoic acid**

Exposure to retinoic acid (which is used in the treatment of acne) is associated with structural brain abnormalities, neuronal migration defects, microtia and complex cardiac malformations.

## **Fetal valproate syndrome**

Fetuses exposed to valproate have an increased risk of cleft lip and palate, neural tube defects, cardiac defects, radial ray defects, learning disability and facial anomalies (frontal narrowing including metopic craniosynostosis, thin eyebrows, infraorbital skin grooves, long philtrum, thin upper lip). These effects appear to be dose dependent.

## **Fetal warfarin syndrome**

Fetuses exposed to warfarin typically have nasal hypoplasia, stippled epiphyses and are at risk of learning disability and brain, eye, cardiac and skeletal malformations.

## **10. PRENATAL TESTING**

- **Chorionic villous sampling or biopsy** (CVS or CVB) – a small piece of placenta is taken either transabdominally or transvaginally. CVS testing can be safely performed from 11 weeks' gestation
- **Amniocentesis** – amniotic fluid is taken, containing cells derived from the surfaces of the fetus and amniotic membranes. Amniocentesis is usually performed from 15 weeks' gestation
- **Cordocentesis** – a method of obtaining fetal blood that can be performed from 18 weeks' gestation

Chromosome and DNA testing can be performed on any of the above types of sample, and

biochemical analyses can often also be performed if necessary. Each method carries a small risk of miscarriage. As a result, most couples opt for prenatal testing only if they wish to terminate an affected pregnancy. Although chromosome analysis can be performed on any pregnancy, DNA analysis can be used only in families where known mutations have already been identified, and the family is at significant risk.

It is possible to identify the sex of an unborn fetus by prenatal testing and, in the case of X-linked conditions where no specific mutation has been identified, this is often the only available prenatal test. However, it is illegal in the UK to terminate a pregnancy on the basis of gender alone unless the child is at risk of a genetic condition due to its gender.

## **11. NON-INVASIVE PRENATAL TESTING**

Cell-free fetal DNA can be detected in the mother's circulating blood from 4 weeks' gestation. The vast majority of the cell-free DNA is maternal, however, so testing is currently limited to the identification or exclusion of genetic material not present in the mother, such as Y chromosome, or rhesus D in RhD-negative women. In those at risk of an X-linked disorder in sons, this process will remove the necessity for invasive testing in 50% of pregnancies. Currently it is not possible to test for trisomy 21 or other chromosomal anomalies by this method.

## **12. PREIMPLANTATION GENETIC DIAGNOSIS**

This technique is an in vitro fertilization (IVF)-based process. At the 8- to 16-cell stage a single cell is removed from each embryo for testing. Only embryos predicted to be unaffected are reimplanted into the mother. Preimplantation genetic testing (PGD) is technically difficult and has a similar viable pregnancy rate to IVF (25%). It is available in the UK for a limited, although increasing, number of conditions and virtually all inherited chromosome anomalies. For funding purposes it is frequently regarded as fertility treatment, so families can find it hard to get NHS treatment. Overseas centres have a wider range of conditions, but it is very expensive.

## **13. GENETIC COUNSELLING**

This is the process of assisting families or individuals affected by genetic disease to understand the cause of their condition, the risk of recurrence and the options available to them. It is entirely non-directive and the aim is to deliver all available information to allow the family to make the appropriate decisions. Some families will opt for prenatal diagnosis and termination, although this will not be acceptable for others. Equally, with predictive testing, not everyone at significant risk of a condition chooses to have testing to clarify this risk further. Genetic counselling will be offered to all, with no obligation to pursue testing.

## **14. FURTHER READING**



- Firth HV, Hurst JA. *Oxford Desk Reference – Clinical Genetics*. Oxford University Press, 2005.
- Harper PS. *Practical Genetic Counselling*, 7th edn. London: Hodder Education, 2010.
- Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 6th edn. Philadelphia: Elsevier Saunders, 2005.
- Kingston HM. *ABC of Clinical Genetics*, 3rd edn. Oxford: Wiley-Blackwell, 2002

---

# Chapter 12

## Haematology and Oncology

*Michael Capra*

---

### CONTENTS

#### **1. Haemoglobin**

- [1.1 Haemoglobin synthesis](#)
- [1.2 Red cell physiology](#)
- [1.3 Oxygen-dissociation curve](#)

#### **2. Haemoglobin abnormalities**

- [2.1 Thalassaemia](#)
- [2.2 Sickle cell disease \(SCD\)](#)
- [2.3 Other haemoglobinopathies](#)

#### **3. Blood group antibodies**

- [3.1 ABO system](#)

#### **4. Blood product transfusion**

- [4.1 Acute blood product transfusion reactions](#)
- [4.2 Massive transfusion reactions](#)

#### **5. Anaemia**

- [5.1 Iron deficiency anaemia](#)
- [5.2 Aplastic anaemia](#)
- [5.3 Hereditary haemolytic anaemias](#)
- [5.4 Haemoglobin defects](#)
- [5.5 Polycythaemia](#)

#### **6. The white cells: phagocytic cells**

- [6.1 Neutrophils](#)

[6.2 Eosinophils](#)

[6.3 Basophils](#)

[6.4 Monocytes](#)

## **[7. The white cells: lymphocytes](#)**

## **[8. Platelets](#)**

[8.1 Thrombocytopenia](#)

[8.2 Immune thrombocytopenic purpura](#)

[8.3 Neonatal isoimmune thrombocytopenia](#)

[8.4 Functional abnormalities of platelets](#)

## **[9. Blood film](#)**

[9.1 Approach to a blood film at MRCPCH level](#)

## **[10. Coagulation](#)**

[10.1 Natural anticoagulants](#)

[10.2 Coagulation disorders](#)

## **[11. Bruising](#)**

[11.1 An approach to bruising in children](#)

## **[12. Malignant pathology](#)**

[12.1 Leukaemia](#)

[12.2 Lymphoma](#)

[12.3 Tumour-lysis syndrome](#)

[12.4 Tumours of the CNS](#)

[12.5 Retinoblastoma](#)

[12.6 Neuroblastoma](#)

[12.7 Wilms tumour \(nephroblastoma\)](#)

[12.8 Bone tumours](#)

[12.9 Soft-tissue sarcomas](#)

[12.10 Malignant germ-cell tumours](#)

[12.11 Hepatoblastoma](#)

[12.12 Langerhans cell histiocytosis](#)

[12.13 Haemophagocytic lymphohistiocytosis](#)

[12.14 Role of bone marrow transplantation](#)

[12.15 Principles of managing malignancy](#)

[12.16 Palliative care](#)

[12.17 Late effects of cancer treatment](#)

## **[13. Further reading](#)**

---

# Haematology and Oncology

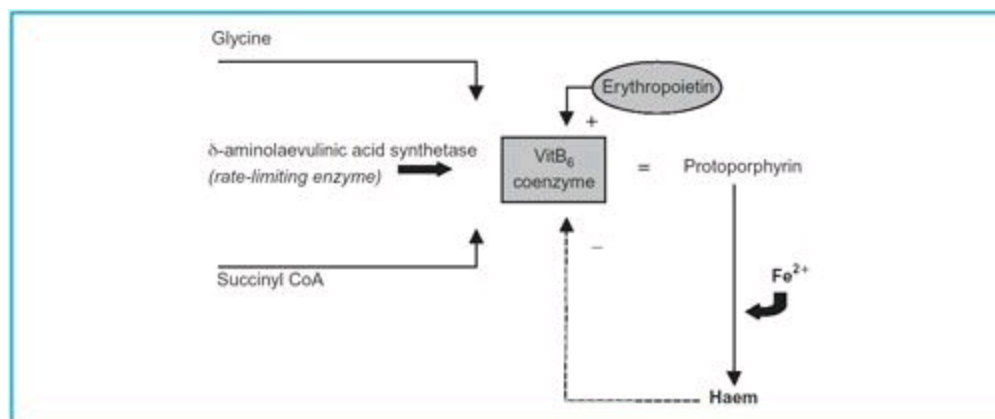
---

## 1. HAEMOGLOBIN

### 1.1 Haemoglobin (Hb) synthesis

Erythropoietic activity is regulated by erythropoietin, a hormone secreted by the peritubular complex of the kidney (90%), the liver and elsewhere (10%). The stimulus to erythropoietin production is the oxygen tension within the kidney. Mitochondria of the developing erythroblast are the main sites for the synthesis of haem:

- The cofactor vitamin B<sub>6</sub> is stimulated by erythropoietin and inhibited by haem
  - The Fe<sup>2+</sup> is supplied by circulating transferrin
- Globin chains, comprising a sequence of polypeptides, are synthesized on ribosomes
- A tetramer of four globin chains, each with its own haem group attached, is formed to make a molecule of haemoglobin



Haem synthesis.

### 1.2 Red cell physiology

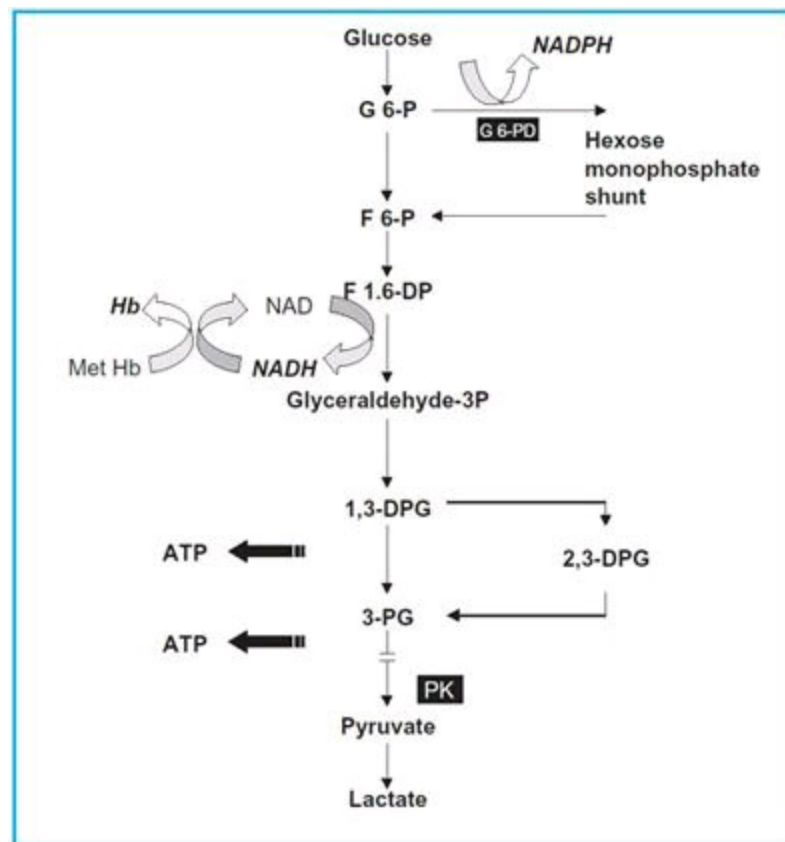
The 8-µm diameter red cell has three challenges:

- To pass through the microcirculation of capillaries (diameters of 3.5 µm)
- To maintain haemoglobin in the reduced state

- To maintain an osmotic equilibrium despite a high concentration of protein (five times that of plasma)

It achieves this by:

- The protein, spectrin, which enables it to have a flexible biconcave disc shape
- Generating reducing power in the form of nicotinamide adenine dinucleotide (NADH) from the Embden–Meyerhof pathway and NAD phosphate (NADPH or reduced NADP<sup>+</sup>) from the hexose monophosphate shunt; this reducing power is vital in preventing oxidation injury to the red cell and for reducing functionally dead methaemoglobin (oxidized haemoglobin) to functionally active, reduced haemoglobin (see figure below)
- Generating energy in the form of ATP from the Embden–Meyerhof pathway; this energy is used to drive the cell membrane Na<sup>+</sup>/K<sup>+</sup> pump to exchange three ions of intracellular Na<sup>+</sup> for two ions of K<sup>+</sup> thus maintaining an osmotic equilibrium
- Generating 2,3-diphosphoglycerate (2,3-DPG) to reversibly bind with haemoglobin to maintain the appropriate affinity for oxygen.



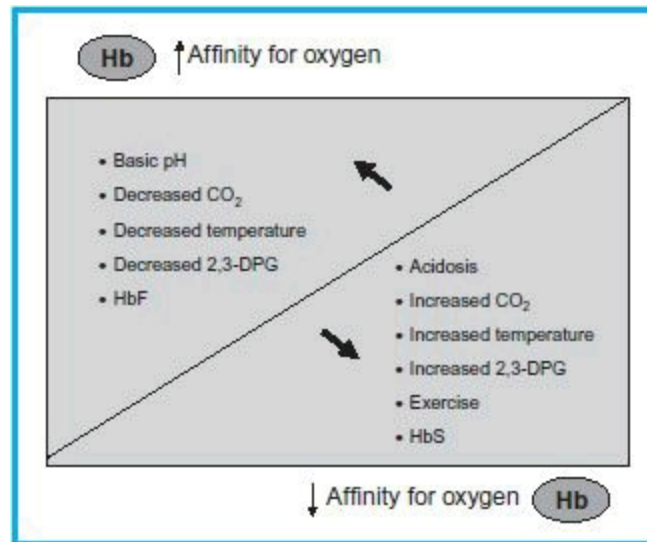
The Embden–Meyerhof and associated pathways.

2,3-DPG, 2,3-diphosphoglycerate; F6-P, fructose 6-phosphate; F1,6-DP, fructose 1,6-diphosphate; G6-P, glucose 6-phosphate; G6-PD, glucose-6-phosphate dehydrogenase; MetHb, methaemoglobin; PK, protein kinase.

## 1.3 Oxygen-dissociation curve

When oxygen is unloaded from a molecule of oxygenated haemoglobin, the  $\beta$  chains open up, allowing 2,3-DPG to enter. This results in the deoxygenated haemoglobin having a low affinity for oxygen, preventing haemoglobin from stealing the oxygen back from the tissues. This 2,3-DPG-related affinity for oxygen gives the oxygen-dissociation curve its almost sinusoidal appearance rather than that of a straight line.

Factors that cause this dissociation curve to shift are summarized in the figure below.



Factors shifting the oxygen-dissociation curve. HbF, fetal haemoglobin; HbS, sickle cell haemoglobin.

Shift of the curve by changes in the blood  $\text{CO}_2$  is important to enhance both oxygenation of the blood in the lungs and = the release of oxygen from the blood to the tissues. This is the **Bohr effect**.

As  $\text{CO}_2$  diffuses from the capillaries into the alveoli within the lungs,  $\text{PCO}_2$  is reduced and the pH increases. Both of these effects cause the curve to shift left and upwards. Therefore the quantity of oxygen that binds with the haemoglobin becomes considerably increased, so allowing greater oxygen transport to the tissues. When the blood reaches the capillaries the exact opposite occurs. The  $\text{CO}_2$  from the tissues diffuses into the blood, decreasing the pH and causing the curve to shift to the right and downwards, i.e. the curve shifts to the right in the tissues and to the left in the lungs.

## 2. HAEMOGLOBIN ABNORMALITIES

These result from the synthesis of an abnormal haemoglobin (haemoglobinopathy) or from a decreased rate of synthesis of normal – or  $\beta$ -globin chains (thalassaemia). The chain structure is determined by a pair of autosomal genes. The genes for  $\beta$ ,  $\alpha$  and  $\gamma$  chains are carried on chromosome 16, whereas chromosome 11 carries the  $\beta$  chain. Haemoglobinopathy and thalassaemia genes are allelomorphs (different genes can occupy the same locus on a chromosome) – which is the reason why mixed haemoglobinopathies can occur in one patient, e.g. HbS and thalassaemia may occur in one patient.

### 2.1 Thalassaemia

Thalassaemia results from a genetically determined imbalanced production of one of the globin chains.  $\beta$ -,  $\alpha$ -,  $\sigma$ - and  $\gamma$ -globin chains make up normal fetal and adult haemoglobin in the following combinations:

- Fetal Hb:
  - HbF – ( $\alpha_2 + \gamma_2$ )
  - Hb Barts –  $\gamma_4$
- Adult Hb:
  - HbA –  $\alpha_2 + \beta_2$  (97%)
  - HbA<sub>2</sub> –  $\alpha_2 + \sigma_2$  (2.5%)

## Haemoglobin types in the different haemoglobinopathies

Disease	Genes	Haemoglobin type present
Sickle cell disease	S/S	S + F
Sickle cell trait	S/A	S + A
HbC disease	C/C	C
HbC trait	C/A	C + A
HbD disease	D/A	D
HbE disease	E/A	E + F
Sickle cell–HbC disease	S/C	S + C + F
Sickle cell–thalassaemia	S $\beta^+$	S + F (also A if $\beta^+$ , if $\beta^0$ then no A)
HbC–thalassaemia	C $\beta^+$	C + F (also A if $\beta^+$ , if $\beta^0$ then no A)
HbE–thalassaemia	E $\beta^+$	E + F (also A if $\beta^+$ , if $\beta^0$ then no A)

## Clinical management of thalassaemia

Safe blood transfusion programmes with effective iron-chelation therapy have transformed the outlook for children with thalassaemia.

## Red cell transfusions

The aim here is to eliminate the complications of anaemia and ineffective erythropoiesis, which will allow the child to grow and develop normally. The decision to start on a transfusion programme can be difficult but generally the recommendation is to start when the haemoglobin concentration is <6.0 g/dl over 3 consecutive months. The desired maintenance haemoglobin level is around 9.5 g/dl, with care being taken not to increase the iron burden too much.

## Chelation treatment

Iron overload is the most important challenge of life-saving transfusions in thalassaemia. Up until the late 1990s parental deferoxamine (DFO) was the only available chelating agent of choice but, over the last decade, particularly in the last 5 years, two oral agents, deferiprone (L1) and deferasirox (DFRA), have been made available. L1 is approved for use in Europe but not in North America. Unfortunately, due to imperfect comparative data, it remains unclear which agent is the most effective with the least toxicity. The oral agents are now widely used, with DFO being used predominantly only in combination.

When to initiate chelation therapy remains unclear but it is recommended that a liver biopsy be performed after 1 year of a transfusion programme to establish the iron burden. Serum ferritin, although helpful, is not entirely accurate especially at the high levels seen in such patients.

## Curative treatment

Up until recently bone marrow transplantation has been the only curative option but this treatment option must be carefully balanced against the morbidity (e.g. graft-versus-host disease) and significant mortality associated with allogeneic transplantation. A recent publication from Italy (see Section 13) reported a 89.2% 20-year overall survival rate for 115 patients with thalassaemia who were treated with allogeneic transplantation. Currently there is some renewed optimism in the possibility of replacement gene therapy for thalassaemia (see Section 13).

## 2.2 Sickle cell disease (SCD)

- It primarily affects people of African, African–Caribbean, Middle Eastern, Indian and Mediterranean descent
- In parts of Africa, 30% of the population have sickle cell trait
- It is caused by a single-base mutation of adenine to thiamine, resulting in a substitution of valine for glutamic acid (at the sixth codon) on the  $\beta$ -globin chain
- HbS is insoluble and forms crystals when exposed to low oxygen tension
- The symptoms of anaemia are mild relative to the severity of the anaemia, as HbS shifts the oxygen–haemoglobin curve to the right (see figure on p. 303)
- It presents after the age of 6 months – the time at which the production of haemoglobin should have switched from HbF to HbA
- The two predominant major pathophysiological processes are vaso-occlusion with ischaemia–reperfusion injury (crises) and haemolytic anaemia.
- Crises may be visceral, aplastic, haemolytic and painful (see below), and are precipitated by infection, acidosis, dehydration and deoxygenation from whatever cause
- Patients are susceptible to infections with pneumococci and *Haemophilus* and *Salmonella* spp. due to possible multiple causes: impaired splenic function, defective complement activation, tissue ischaemia and micronutrient deficiencies.

## General management

- Neonatal screening programmes are now available, including in USA and England, facilitating early access to a comprehensive sickle cell programme including antibiotic (penicillin) prophylaxis, parental education and early identification of complications.
- Hydroxyurea, a well-tolerated oral cytotoxic agent, increases HbF concentrations which is beneficial to patients with HbS and has proven efficacy in reducing complications of sickle cell disease. Long-term toxicity is still to be determined.
- Blood transfusion plays an important role by correcting anaemia, suppressing HbS synthesis, decreasing HbS percentages and reducing haemolysis. If rapid decrease in HbS is required (e.g. in acute neurological complications) an exchange transfusion may be indicated.



- Bone marrow transplantation (BMT) is the only known curative treatment but not commonly performed because the risk of BMT-related morbidity and mortality is high (mortality rate in the region of 7%).
- Gene therapy remains experimental although promising

## Specific management

- Acute pain – secondary to vaso-occlusive crises – is the most frequent complication of sickle cell disease. Opiate analgesia is the mainstay of treatment
- Infection risk – penicillin prophylaxis and conjugate vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* minimize this risk substantially
- Neurological complications – sickle cell disease is the most common cause of stroke in childhood due to the underlying vasculopathy. Transcranial Doppler ultrasonography can detect vasculopathy at an early stage, facilitating preventive management with regular blood transfusions (see STOP study, see Section 13). Progressive vasculopathy predisposes to moyamoya-like syndrome in young children whereas acute intracranial haemorrhages are more common over the age of 20 years. Cognitive deficits may be due to silent brain infarcts
- Acute chest syndrome – defined as a new pulmonary infiltrate involving at least one lung segment caused by a combination of infection, fat embolism and vaso-occlusion of pulmonary vasculature. It is potentially fatal and requires acute intervention, including assisted ventilation, blood transfusion, oxygen, antibiotics, bronchodilators, and possibly dexamethasone and/or bronchodilators
- Aplastic crisis – coexisting red cell production reduction in the background of chronic haemolysis, often associated with parvovirus infection. Treatment is by blood transfusion

## 2.3 Other haemoglobinopathies

### Sickle cell trait

Individuals are usually asymptomatic as long as they are maintained with good oxygenation – an important point during anaesthesia.

### HbC disease

- Is the result of a substitution of lysine for glutamic acid in the  $\beta$ -globin chain at the same point as the substitution in HbS
- Milder clinical course than HbS
- Prevalent in West Africa

### HbD and HbE disease

- HbD is prevalent on the north-west coast of India, whereas HbE is in south-east Asia – both demonstrate mild anaemia only

## Sickle cell–HbC disease

- Typically has a similar clinical picture to that of HbS, although fewer infections and fewer crises are described
- Associated with avascular necrosis of the femoral head and vascular retinal changes

## Asplenia

- Definition – loss of splenic function can be partial (splenic hypofunction) or complete (asplenia)
- Causes – surgical resection of the spleen, autosplenectomy (due to infarction secondary to haemoglobinopathy), congenital (e.g. Ivemark [asplenia] syndrome)
- Management – there are four important management areas:
  - Penicillin is the antibiotic of choice – given twice a day. When to discontinue prophylactic antibiotics remains controversial. Some centres discontinue at 5 years of age whereas others continue for life
  - Appropriate immunization – routine immunization should be followed. In addition, pneumococcal and meningococcal immunization is recommended. For pneumococcal immunization in children aged <2 years use conjugated heptavalent; in children aged >2 years use 23-valent conjugated immunization. For meningococcal immunization use polysaccharide quadrivalent immunization (note that this does not offer protection against *Neisseria meningitidis* serogroup B)
  - Aggressive management of suspected infection – patients with suspected infection must be evaluated promptly, appropriate specimens for bacterial culture must be obtained and empirical intravenous broad-spectrum antibiotics should be commenced
  - Parent education – parents must be educated to seek medical assistance immediately on suspicion of an infection and must be informed of the potential life-threatening complications of such infections

## 3. BLOOD GROUP ANTIBODIES

Approximately 400 red blood cell group antigens have been described, of which the ABO and rhesus (Rh) groups are of major clinical significance. Kell, Duffy, Kidd and Lutheran groups occasionally cause reactions, while the remaining groups rarely do.

### 3.1 ABO system

This consists of three allelic genes – *A*, *B* and *O*. Each gene codes for a specific enzyme that will result in the production of a carbohydrate residue. This residue will attach itself to one of the three respective lipid and sugar chains – H-antigen, A-antigen and B-antigen chains on the red cell membrane. The *O* gene is an amorph and therefore does not transform the H antigen.

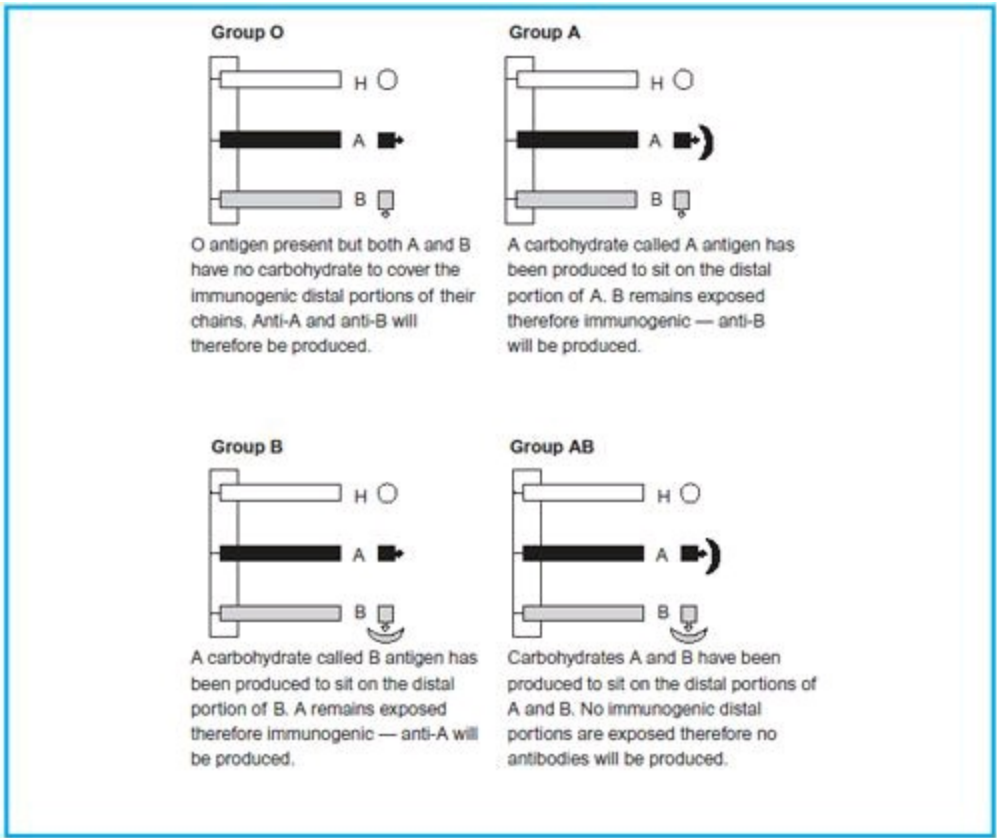
The *A* gene encodes for a carbohydrate residue that will attach itself to the end of the *A*-antigen chain, thereby blocking the distal glycoprotein antigenic portion. Similarly, the *B* gene encodes for a

carbohydrate residue that will block the antigenic portion of the chain (see figure on p. 307).

## ABO blood groups

### A, B, AB and O blood groups

Group	O	A	B	AB
Genotype	OO	AA or AO	BB or BO	AB
Antigens	O	A	B	AB
Naturally occurring antibodies	Anti-A and anti-B	Anti-B	Anti-A	None
Frequency in the UK (%)	46	42	9	3



A, B, AB and O blood groups.

## 4. BLOOD PRODUCT TRANSFUSION

Paediatricians prescribing, and administering, blood product transfusions must be familiar with the principles of blood product replacement therapy and how to manage adverse transfusion reactions.

Serious or life-threatening acute reactions are rare; however, new symptoms or signs that occur during a transfusion must be taken seriously because they may be the first warning of a serious reaction.

### 4.1 Acute blood product transfusion reactions

## **Haemolytic reaction (ABO incompatibility)**

- Antibodies in the recipient's plasma are directed against antigens present on donor red cells
- Usually most severe in group A blood transfused into a group O recipient
- Results in haemolysis, disseminated intravascular coagulation, renal failure and possible complement-mediated cardiovascular collapse
- ABO incompatibility following an administrative or clerical error is the most likely cause

## **Bacterially contaminated infusion**

- Causes severe acute reaction with rapid onset of hypotension, rigors and circulatory collapse

## **Transfusion-related acute lung injury (TRALI)**

- Acute onset of breathlessness, non-productive cough
- Chest X-ray demonstrates bilateral infiltrates
- Clinical characteristics are in keeping with acute respiratory distress syndrome, so treat as such
- Caused by donor antibodies reacting with recipient's leukocytes

## **Non-haemolytic febrile reaction**

- Results from the production of cytokines by donor leukocytes in the transfused blood (performed at the time of the infusion) or from an interaction between leukocyte and anti-leukocyte antibodies in the recipient
- Usually seen after platelet transfusions but may occur with red cell transfusions
- Symptom complex includes: fever, chills and rigors

## **Anaphylactic reaction**

- A rare but life-threatening complication
- Increased risk with transfusion containing large volumes of plasma, e.g. fresh frozen plasma or platelets
- Clinical presentation – hypotension, bronchospasm, periorbital and laryngeal oedema, vomiting, erythema, urticaria, conjunctivitis, dyspnoea, chest/abdominal pain
- Occurs in patients presensitized to allergen-producing immunoglobulin E (IgE) antibodies, less commonly with IgG or IgA antibodies

## **4.2 Massive transfusion reactions**

A massive transfusion, defined as replacement of more than half of the patient's blood volume at one time or the replacement of the entire blood volume within a 24-hour period, may be complicated by:

- Coagulopathy (secondary to a relative thrombocytopenia and platelet dysfunction)

- Volume overload
- Hypothermia
- Hypokalaemia (the potassium-depleted donor's red cells have the ability to absorb serum potassium)
- Hypocalcaemia (secondary to citrate toxicity – citrate is used as an anticoagulant to prevent coagulation of stored blood)

## Details of blood products for transfusion

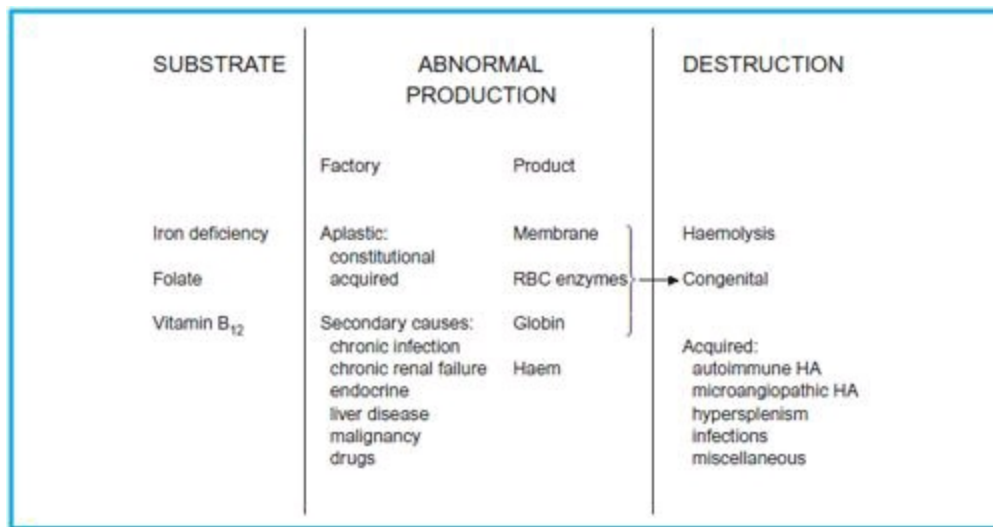
Blood product	Indication	Content description	Dose	Predicted increment	Special precautions
Packed RBC	Correct inadequate tissue O <sub>2</sub> delivery	RBC concentrate	10–15 ml/kg	2–3 g/dl	Cross-match Must be ABO compatible
Fresh frozen plasma	Coagulopathy DIC Warfarin reversal Vitamin K deficiency	All coagulation factors and complement	10 ml/kg		Should be ABO compatible
Cryoprecipitate	vWD hypo-fibrinogemia F XIII deficiency	10 ml contains > 80 U F VIII and > 150 mg fibrinogen	10–50 ml/kg		Should be ABO compatible
Platelet concentrate	Thrombocytopenia	$6.5 \times 10^{10}$ platelets/U	1 U/5 kg max. 6 U	$5 \times 10^9$ to $10 \times 10^9/l$	Should be ABO compatible Monitor recipient's response

RBC, red blood cells; U, unit; DIC, disseminated intravascular coagulopathy; vWD, von Willebrand disease; F VIII, factor VIII; F XIII, factor XIII.

## 5. ANAEMIA

Anaemia results when the oxygen-carrying capacity of the blood is decreased. This is generally caused by having fewer than the normal number of red blood cells (either decreased production or increased destruction of red cells) or less than the normal quantity of haemoglobin in the blood. This definition helps us to formulate the following simple working classification of anaemia, thereby aiding the necessary work up of such patients:

- decreased substrate
- abnormal production of red cells
- abnormal destruction of red cells



Working classification of anaemia.

## 5.1 Iron deficiency anaemia

The major part of body iron is in the form of haem – essential for the delivery of oxygen to the tissues. Iron can exist in both the reduced (electron-gain) and the oxidized (electron-loss) state, the vital property for electron transfer reactions. A useful mnemonic is LEO – loss of an electron is oxidation. As iron is a major constituent of many important respiratory chain enzymes it is therefore directly involved in the production of cellular energy in the form of ATP. Deficiency of iron results in widespread non-haematological effects, e.g. reduced central nervous system (CNS) higher functions, diminished T-cell function and cell-mediated immunity, as well as diminished muscle performance.

- Iron deficiency anaemia (Hb <11 g/dl) occurs in 10–30% of preschool children living in inner cities in the UK

### Causes of iron deficiency

- Dietary insufficiency, e.g. unfortified milk
- Increased physiological requirement – infancy/adolescence
- Blood loss – gastrointestinal
- Malabsorption – coeliac disease

The most common reason in infancy is the early weaning to cows' milk. Giving an infant iron-supplemented formula milk instead of cows' milk not only prevents anaemia but reduces the decline in developmental performance observed in those given only cows' milk.

### Causes of a microcytic anaemia

Definition: mean corpuscular (or cell) volume (MCV) <72 fl in children <2 years or <78 fl in older children (where fl = femtolitres).

Causes include:

- Iron deficiency
- Anaemia of chronic disorders – infection, malignancy
- Disorders of globin synthesis – thalassaemia trait, homozygous haemoglobinopathies
- Lead poisoning
- Sideroblastic anaemia

## 5.2 Aplastic anaemia

### Classification of aplastic anaemia

- Constitutional (30%):
  - Fanconi anaemia
  - Familial marrow aplasia in association with hand anomalies, deafness, ataxia, immune deficiencies
  - Dyskeratosis congenita – ectodermal dysplasia, X linked
  - Shwachman–Diamond syndrome – pancreatic insufficiency
  - Amegakaryocytic thrombocytopenia
  - Reticular dysgenesis
- Acquired:
  - Idiopathic – majority of cases
  - Drugs, e.g. acetazolamide, chloramphenicol
  - Infections, e.g. Epstein–Barr virus (EBV), viral hepatitis, parvovirus
  - Toxins, e.g. glues, dichlorodiphenyltrichloroethane (DDT)
  - Paroxysmal nocturnal haemoglobinuria

Steroids and/or anti-thymocyte globulin has some beneficial effects in a few cases. The prognosis is invariably poor in severe cases, with bone marrow transplantation the only viable treatment option available.

## 5.3 Hereditary haemolytic anaemias

For an understanding of hereditary haemolytic anaemias, one has to consider the membrane, red cell enzyme and haemoglobin defects involved.

### Membrane defects

#### Hereditary spherocytosis

- The most common hereditary haemolytic anaemia in north Europeans
- Autosomal dominant
- Complex defect but involves the spectrin structural protein

- Diagnosis made on appearances of blood film – the presence of spherocytes identified by demonstrating that the cells are osmotically active using the osmotic fragility test
- The serum bilirubin and lactate dehydrogenase (LDH) may be elevated
- Treatment, by splenectomy, is reserved for severe cases

## **Hereditary elliptocytosis**

- Usually autosomal dominant
- Most cases are asymptomatic

## **Red cell enzyme defects**

Although a deficiency of any enzyme involved in the Embden–Meyerhof pathway may cause haemolysis, the two most commonly occurring deficiencies are as follows.

### **Glucose-6-phosphate dehydrogenase (G6PD) deficiency**

- G6PD helps to maintain glutathione in a reduced state, thus protecting the red cell from oxidative injury
- It is X linked
- Different mutations of the gene are all found in different racial groups – black Africans: 10% incidence; Mediterranean races: up to 35% incidence
- Neonatal jaundice may be the first sign
- Precipitating causes include infections, acidosis, favism, drugs
- Diagnose by assaying G6PD enzyme

Drugs to avoid in G6PD deficiency are:

- Analgesics/antipyretics: aspirin, probenecid
- Antimalarials: chloroquine
- Sulphonamides: dapsone
- Antibiotics: co-trimoxazole, nitrofurantoin, nalidixic acid, chloramphenicol
- Cardiovascular drugs: procainamide
- Miscellaneous: ascorbic acid, methyldopa, urate oxidase

### **Pyruvate kinase (PK) deficiency**

- Deficiency of PK blocks the Embden–Meyerhof pathway – see figure on p. 302)
- PK deficiency causes a rise in 2,3-DPG, which causes a shift to the right on the oxygen-dissociation curve and consequent improvement in oxygen availability (see figure on p. 303). Patients can therefore tolerate very low Hb levels
- It is autosomal recessive
- Infections, especially parvovirus, can produce dramatic haemolysis
- Splenectomy may be beneficial



## 5.4 Haemoglobin defects

See also Section 2 – Haemoglobin abnormalities.

### **Autoimmune haemolytic anaemia (AIHA)**

- Coombs test (anti-human globulin) positive (see opposite)
- Uncommon in childhood, but if present is usually the result of an intercurrent infection – predominantly viral but occasionally mycoplasmal in origin
- In the older child, AIHA may be a manifestation of a multisystem disease, e.g. systemic lupus erythematosus (SLE)
- Causes include drugs (high-dose penicillin), infections (non-specific viral, measles, varicella, EBV), multisystem disease (SLE, rheumatoid arthritis) and lymphoproliferative disease (Hodgkin lymphoma)
- Can be divided into warm and cold types depending on the temperature at which the causative cell-bound antibody is best detected:
  - Warm (usually IgG) – multisystem disease
  - Cold (usually IgM) – infective causes

### **Microangiopathic haemolytic anaemia**

- A rapidly developing haemolytic anaemia with fragmented red cells and thrombocytopenia
- Occurs in haemolytic–uraemic syndrome and thrombotic thrombocytopenic purpura

### **Hypersplenism**

- The red cell lifespan is decreased by sequestration in an enlarged spleen for whatever cause

### **Infections**

- Malaria
- Septicaemia

### **Miscellaneous**

- Burns
- Poisoning
- Hyperphosphataemia
- Abetalipoproteinaemia

### **The Coombs (antiglobulin) test**

Anti-human globulin (AHG) is produced in many animal species after the injection of human globulin.

When AHG is added to human red cells that have been coated (sensitized) by immunoglobulin or complement components, agglutination of the red cells will occur, indicating a positive test.

There are two anti-globulin tests.

### **Direct antiglobulin test**

This is used to detect antibody or complement on the red cell surface where sensitization has occurred in vivo.

A positive test occurs in:

- Haemolytic disease of the newborn
- Autoimmune haemolytic anaemia
- Drug-induced immune haemolytic anaemia
- Haemolytic transfusion reactions

### **Indirect antiglobulin test**

This is used to detect antibodies that have coated the red cells in vitro. It is a two-stage procedure. The first stage involves incubation of test red cells with serum. The second stage involves washing these red cells with saline to remove free globulins. AHG is then added to the washed red cells. Agglutination implies that the original serum contained antibody, which has coated the red cells in vitro.

This indirect antiglobulin test is used in the following circumstances:

- Routine cross-matching procedures – to detect antibodies in the patient's serum that will be directed towards the donor red cells
- Detecting atypical blood group antibodies in serum during screening procedures
- Detecting blood group antibodies in a pregnant woman
- Detecting antibodies in serum in autoimmune haemolytic anaemia

## **5.5 Polycythaemia**

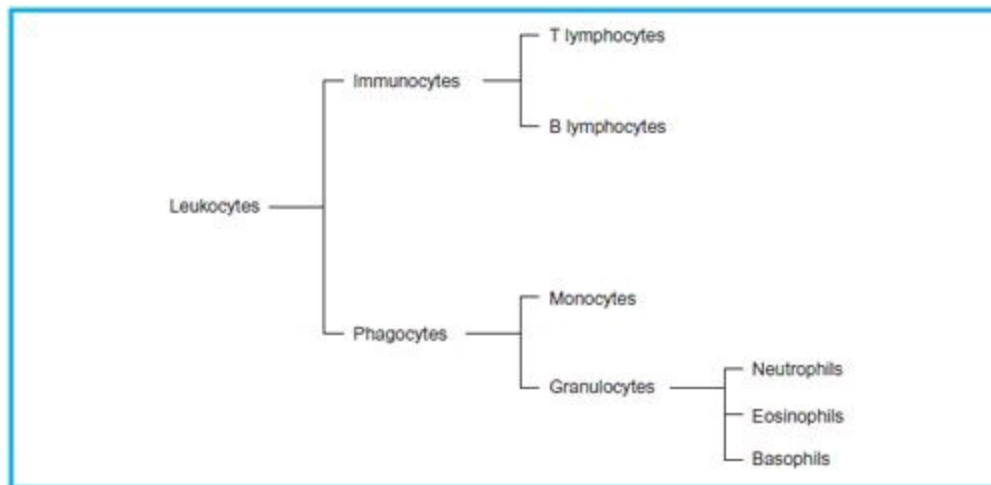
Defined as an increase in the absolute quantity of red cells or total RBC volume when haematocrit is  $\geq 65\%$ . It is classified into:

- Primary (rare in childhood) – due to factors intrinsic to the red cell precursor, predominantly encompassing specific mutations in the erythrocyte receptor: primary familial and congenital polycythaemia, polycythaemia vera (part of the myeloproliferative syndrome)
- Secondary – due to factors outside of the red cell
  - Response to tissue hypoxia with increased erythropoietin production:
    - Heart disease – congenital cyanotic cardiac defects, e.g. tetralogy of Fallot
    - Lung disease
    - Increased altitude

- High-oxygen affinity haemoglobinopathies, e.g. congenital methaemoglobinaemia
- Neonatal period – polycythaemia is common within the first 6–12 h after birth, usually resolving by 24 h. It is more common in small- or large-for-gestational age infants or when there has been delayed clamping of the cord
- Ectopic production of erythropoietin
  - Renal disease, e.g. polycystic kidneys, Wilms tumour
  - Liver disease, e.g. hepatocellular carcinoma

Polycythaemia causes hyperviscosity which in turn may lead to diminished blood flow to organs with CNS, cardiopulmonary, GI and renal systems most at risk. Metabolic disturbances, predominantly of glucose and calcium, may be seen and coagulation may be affected. Treatment includes intravenous fluids (in neonatal period, partial exchange transfusion may be of benefit) and monitoring of glucose and calcium levels.

## 6. THE WHITE CELLS: PHAGOCYtic CELLS



White cells or leukocytes can broadly be classified into groups.

The primary function of the white cells, together with immunoglobulins and complement, is to protect the body against infection.

**Granulocytes** and **monocytes** comprise the phagocytic (myeloid) group of white cells. They originate from a common precursor cell. It takes between 6 and 10 days for the precursor cell to undergo mitosis and maturation within the bone marrow. The immature **neutrophil** remains in the bone marrow as a reserve pool until required in peripheral blood. Bone marrow normally contains more myeloid than erythroid precursors – in a ratio of up to 12:1 and between 10 and 15 times more the number of granulocytes than in peripheral blood. Granulocytes spend only a matter of hours within the bloodstream before going into tissues. There are two pools of cells within the bloodstream – the circulating pool (what is included in the blood count) and the marginating pool (not included in the blood count as these cells adhere to the endothelium).

### Formation, proliferation, differentiation and function

Growth factors are produced in stromal cells (endothelial cells, fibroblasts and macrophages) and from T lymphocytes. Under the influence of specific growth factors – stem-cell factor, interleukin-1 (IL-1), IL-3 and IL-6 – a haematopoietic stem cell is produced. Granulocyte–monocyte colony-stimulating factor (GM-CSF) increases the commitment of this stem cell to differentiate into a **phagocyte**. Further differentiating and proliferating stimulus is required from G-CSF for **neutrophil** production, from IL-5 for **eosinophil** production and from M-CSF for **monocyte** production.

In addition, growth factors affect the function of the mature myeloid cells:

- Optimizing phagocytosis, superoxide generation and cytotoxicity in the neutrophil
- Optimizing phagocytosis, cytotoxicity and production of other cytokines in the monocyte
- Increasing membrane integrity and surface-adhesion properties of target cells
- GM-CSF can immobilize phagocytes at local sites of inflammation thereby causing accumulation at these sites

## 6.1 Neutrophils

### Neutropenia

Neutropenia is defined as a reduction of the absolute neutrophil count below the normal for age.

Neutropenia can be divided according to the severity, indicating the likely clinical consequences:

- Mild:  $1.0\text{--}1.5$  ( $10^9/\text{l}$ ) – usually no problem
- Moderate:  $0.5\text{--}1.0$  ( $10^9/\text{l}$ ) – clinical problems more common
- Severe:  $<0.5$  ( $10^9/\text{l}$ ) – potentially severe and life threatening, especially if prolonged beyond a few days

Bacterial infections such as cellulitis, superficial and deep abscess formation, pneumonia and septicaemia are the most common problems associated with isolated neutropenia, whereas fungal, viral and parasitic infections are relatively uncommon.

The typical inflammatory response may be greatly modified with poor localization of infection, resulting in a greater tendency for infection to disseminate.

### The normal range of white blood cell (WBC) and neutrophil counts for children at different ages

Age	Total WBC $\times 10^9/\text{l}$		Neutrophils $\times 10^9/\text{l}$		%
	Mean	Range	Mean	Range	
Birth	18	9.0–30	11	6.0–26	61
1 week	12	5.0–21	5.5	1.5–10	45
1 month	10.8	5.0–19.5	3.8	1.0–9	35
6 months	11.9	6.0–17.5	3.8	1.0–8.5	32
1 year	11.4	6.0–17.5	3.5	1.5–8.5	31
6 years	8.5	5.0–14	4.3	1.5–8	51
16 years	7.8	4.5–13	4.4	1.8–8	57

Although challenging in some cases, it is important to identify the cause of the neutropenia, see following box, especially for the two following reasons:

- The clinical significance of the neutropenia will depend upon whether or not there is underlying marrow reserve
- Identifying the cause can help in predicting the duration of the neutropenia and therefore effect subsequent management

Marrow suppression (decreased production) will usually cause a severe neutropenia. The majority of children treated with chemotherapy will be in this group. Increased consumption or sequestration will cause mild to moderate neutropenia.

Causes of neutropenia	
Decreased marrow production	
Congenital	Acquired
Kostmann syndrome	Aplastic anaemia
Reticular dysgenesis	Fanconi anaemia
	Drug suppression
	Cyclical neutropenia
	Vitamin B <sub>12</sub> , folate,
	copper deficiency
	Chronic benign neutropenia
	Myelofibrosis
	Osteopetrosis
Export	
Metabolic conditions:	
Propionic, isovaleric and methylmalonic acidaemia	
Hyperglycinaemia	
Consumption	
Autoimmune antibodies	
Neonatal isoimmune haemolytic disease	
Infection/endotoxaemia	
Sequestration	

Immune complexes  
Viral  
SLE  
Felty syndrome  
Sjögren syndrome  
Hypersplenism

### **Associated with immune deficiency**

X-linked hypogammaglobulinaemia  
Selective immunoglobulin deficiency states

### **Associated with phenotypically abnormal syndromes**

Shwachman syndrome  
Chédiak–Higashi syndrome  
Cartilage hair hypoplasia  
Dyskeratosis congenita

The risk of infection is directly proportional to the duration of neutropenia. If the duration of neutropenia is predicted to be prolonged, preventive measures against possible future infective episodes may be considered, e.g.:

- Good mouth care and dental hygiene
- Prophylaxis against *Pneumocystis* spp. (co-trimoxazole)
- Prophylaxis against fungal infections (fluconazole)
- Prophylaxis against recurrent herpes simplex virus infection (aciclovir)
- Regular throat and rectal swabs looking for Gram-negative colonization
- Dietary avoidance of unpasteurized milk and salads
- Avoidance of inhaling building/construction dust because of the risk of acquiring aspergillus infection

## **Neutrophilia**

The neutrophil count can be increased in one of the following three ways:

- Increased production of neutrophils as a result of increased progenitor cell proliferation or an increased frequency of cell division of committed neutrophil precursors
- Prolonged neutrophil survival within the plasma as a result of impaired transit into tissues
- Increased mobilization of neutrophils from the marginating pools or bone marrow

### **Acute neutrophilia**

Neutrophils can be mobilized very quickly, within 20 minutes of being triggered, from the marginating pool. A stress response (acute bacterial infection, stress, exercise, seizures and some toxic agents) releases adrenaline (epinephrine) from endothelial cells, which decreases neutrophil adhesion. This

results in the neutrophils adhering to the endothelial lining of the vasculature (the marginating pool) being dragged into the circulation.

The bone marrow storage pool responds somewhat slower (a few hours) in delivering neutrophils in response to endotoxins, released from microorganisms, or complement.

Corticosteroids may inhibit the passage of neutrophils into tissues, thereby increasing the circulating number.

### **Chronic neutrophilia**

The mechanism in chronic neutrophilia is usually an increased marrow myeloid progenitor-cell proliferation. The majority of reactions last a few days or weeks. Infections and chronic inflammatory conditions (e.g. juvenile chronic arthritis, Kawasaki disease) are the predominant stimulators of this reaction. Less common causes include malignancy, haemolysis or chronic blood loss, burns, uraemia and postoperative states.

Splenectomy or hyposplenism may result in a reduced removal of increased neutrophils from the circulation.

## **6.2 Eosinophils**

Eosinophils enter inflammatory exudates and have a special role in allergic responses, in defence against parasites and in removal of fibrin formed during inflammation. Eosinophils are proportionately reduced in number during the neonatal period. The causes of eosinophilia are extensive but some of the major causes are:

- Allergic diseases, e.g. asthma, hay fever, urticaria
- Parasitic diseases, e.g. worm infestation
- Recovery from infection
- Certain skin diseases, e.g. psoriasis, dermatitis herpetiformis
- Pulmonary eosinophilia
- Drug sensitivity
- Polyarteritis nodosa
- Hodgkin disease

## **6.3 Basophils**

Basophils, the least common of the granulocytes, are seldom seen in normal peripheral blood. In tissues they become mast cells. They have attachment sites on their cell membrane for IgE – which, when attaching, will cause degranulation to occur resulting in the release of histamine.

## 6.4 Monocytes

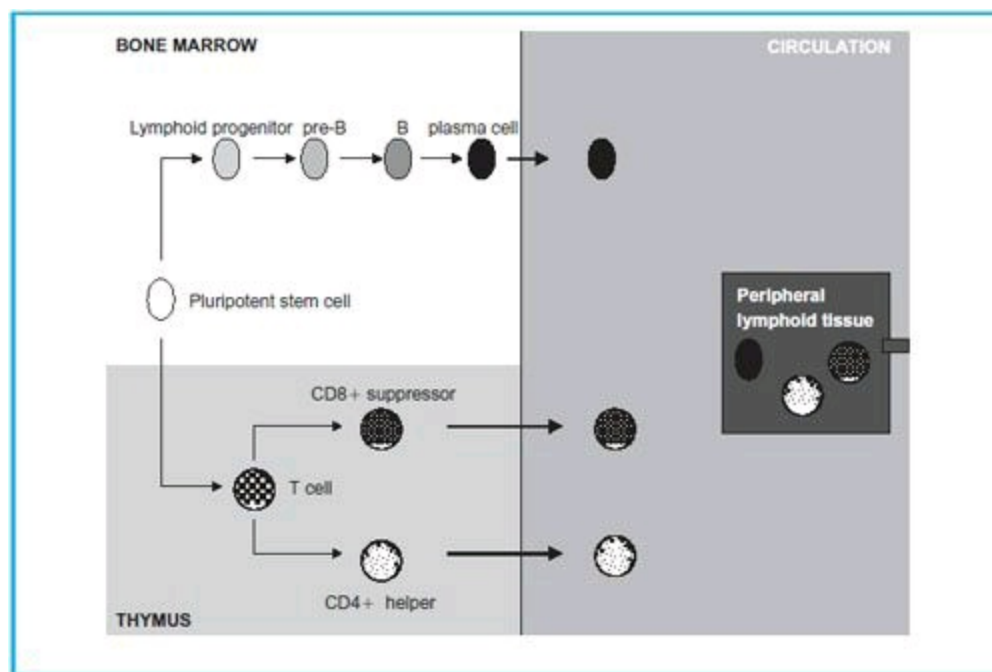
Monocytes, the largest of the leukocytes, spend a short time in the bone marrow and an even shorter time in the circulation (20–40 hours) before entering tissues where the final maturation to a phagocyte takes place. A mature phagocyte has a lifespan of months to years.

## 7. THE WHITE CELLS: LYMPHOCYTES

Lymphocytes, divided into **T lymphocytes** and **B lymphocytes**, are the immunologically active cells which help the phagocytes to defend the body from an infective or other foreign invasion by aiding specificity.

### Formation

The bone marrow and thymus are the two primary sites in which lymphocytes are produced, not by specific antigens but by non-specific cytokines. Thereafter they undergo specific transformation in secondary or reactive lymphoid tissue – the lymph nodes, spleen, the circulating lymphocytes and the specialized lymphoid tissue found in the respiratory and gastrointestinal tracts.



Diagrammatic illustration of immunocyte production.

T cells are produced in the bone marrow and undergo transformation in the thymus, whereas the exact location where the B lymphocytes are transformed remains unknown.

In peripheral blood 80% of the lymphocytes are T cells, whereas only 20% are B cells. T cells are responsible for cell-mediated immunity (against intracellular organisms and transplanted organs). B cells and plasma cells (differentiated B cells) are responsible for humoral immunity by producing immunoglobulins.



## 8. PLATELETS

Megakaryocytes, produced in the bone marrow, develop into platelets by a unique process of cytoplasm shedding. As the megakaryocyte matures the cytoplasm becomes more granular; these granules develop into platelets and are released into the circulation as the cytoplasm is shed.

Platelet production is under the control of growth factors, particularly thrombopoietin and IL-6, whereas GM-CSF and IL-3 have megakaryocyte CSF (MG-CSF) properties.

The main function of platelets is the formation of mechanical plugs during the normal haemostatic response to vascular injury.

### 8.1 Thrombocytopenia

A useful classification of thrombocytopenia is listed in the box.

#### Thrombocytopenia – causes

##### Impaired production

- Congenital
- Thrombocytopenia and absent radius (TAR) syndrome
- Fanconi anaemia
- Wiskott–Aldrich syndrome
- Acquired:
  - Aplastic anaemia
  - Bone marrow replacement, for example infiltration by malignant disease

##### Decreased platelet survival

- Immune mediated:
  - Immune (idiopathic) thrombocytopenic purpura (ITP)
  - Neonatal isoimmune thrombocytopenia
  - Alloimmune neonatal thrombocytopenia
  - Neonatal ITP
  - Infections
  - Drug induced
  - Autoimmune disorders (e.g. SLE)
  - Malignancy
- Non-immune mediated:
  - Disseminated intravascular coagulation
  - Haemolytic–uraemic syndrome
  - Thrombotic thrombocytopenic purpura (TTP)

- Kasabach–Merritt syndrome
- Cyanotic congenital heart disease
- Liver disease
- Drug-induced
- Miscellaneous

## 8.2 Immune thrombocytopenic purpura

Immune thrombocytopenic purpura is a generic term used to describe an immune-mediated thrombocytopenia that is not associated with drugs or other evidence of disease. It may follow a viral infection or have no antecedent illness. It is caused by an inappropriate response of the immune system, mediated by an IgG autoantibody, although the exact mechanism remains poorly understood.

ITP does not have a predictable course, although it usually follows a benign self-limiting course. Approximately 20% of cases, in older girls predominantly, fail to remit over 6 months (chronic ITP).

### Investigations

Bone marrow examination is not indicated in a typical case (blood counts are normal apart from the platelet count, blood smear confirms no abnormal cells and no splenomegaly is present). However, if corticosteroids are to be used for treatment it is recommended to perform a bone marrow to confirm that there is no underlying acute leukaemia because corticosteroids are lympholytic and therefore may delay or mask this important diagnosis.

### Management

- No data exist to suggest the treatment of acute ITP alters the course of the illness
- Written information about ITP, sensible advice (avoidance of contact sports, what to do in the event of an accident, etc.) and a contact person to call are usually sufficient
- Treatment to raise the platelet count is not always required as the few remaining platelets, even if profoundly low in number ( $<10 \times 10^9/l$ ), function more efficiently due to an increased platelet volume (bigger platelets). The risk of serious bleeding from ITP, compared with that from thrombocytopenia related to marrow failure syndromes, is low
- Patients with ITP may bleed from any site particularly when the platelet counts is  $<10 \times 10^9/l$ . The risk of severe bleeding is very low – 0.6% of patients with a platelet count  $<20 \times 10^9/l$ , with the risk of intracranial haemorrhage (ICH) in the region of 0.1–0.2%. Patients who have ITP and a headache warrant a CT brain scan to exclude ICH. Patients with mucosal bleeding, overt petechiae and ecchymoses should be considered at high risk of bleeding even if platelet counts are  $>20 \times 10^9/l$

Treatment includes the following modalities.

#### Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is the treatment of choice in severe haemorrhage because it raises the platelet count the fastest – usually within 48 hours. The most practical and effective administration of IVIG is a single dose of 0.8 g/kg, although side effects are common at this dose. Traditionally, 0.4 g/kg per day has been given over 5 days.

Side effects with IVIG are common and, as IVIG is a pooled blood product, a risk of viral transmission does exist.

### **Steroids**

Given at a dose of 1–2 mg/kg daily for up to 2 weeks. There is evidence that a higher dose of 4 mg/kg for 4 days may raise the platelet count as quickly as IVIG.

### **Anti-D**

This has been shown to be effective in children who are Rh positive. It is a rapid single injection, although it may cause significant haemolysis.

### **Splenectomy**

Rarely required and is only indicated in a patient with chronic ITP who has significant bleeding unresponsive to medical treatment. The failure rate after splenectomy is at least 25%.

### **Transfusions**

Platelet transfusions are generally not indicated in ITP because it is a consumptive disorder.

### **Cost of treatment**

IVIG is the most expensive, approximately £5550 for a 40-kg child for a total dose of 2 g/kg compared with £1900 for anti-D (75 µg/kg) and £3/day for steroids.

### **Other agents**

In addition to the above, ε-aminocaproic acid may be useful in the uncommon event of a patient with recurrent epistaxis, menstrual or gastrointestinal bleeding. Vincristine, cyclophosphamide and ciclosporin have all been used with varying degrees of success. The combination of cyclophosphamide and rituximab (an anti-CD20 antibody) is currently demonstrating promising results.

### **Neonatal isoimmune thrombocytopenia**

Babies may be born thrombocytopenic as a result of the transplacental passage of maternal antiplatelet antibodies. This can occur in two ways.

### **Alloimmune neonatal thrombocytopenia (ANT)**

- Maternal antibodies are produced as a result of direct sensitization to fetal platelets (analogous to haemolytic disease of the newborn)
- Nineteen human platelet alloantigen (HPA) systems have been documented, the most important one being HPA-1a, causing 85% of ANT cases. Only 3% of the population do not express HPA-1a, so, if a mother does not express HPA-1a, the chances of her partner expressing HPA-1a is high – resulting in an HPA-1a-positive fetus. Only 6% of such mothers will become sensitized, and then

not all sensitized mothers will produce a thrombocytopenic baby

- Antibodies against HPA-1a are IgG and can therefore cross the placenta, bind to fetal platelets and decrease their survival time
- Not only is it possible but it is common for ANT to occur in the first born
- The diagnosis of ANT is suspected when a low platelet count is demonstrated in an otherwise healthy term neonate with a normal clotting screen
- Treatment is in the form of an urgent platelet transfusion if severe (platelet count  $<20 \times 10^9/l$ ) because the risk of an intracerebral bleed is high in the first few days of life. IVIG may play a role in elevating platelet count too, although there is no convincing evidence for the use of corticosteroids
- Treatment of the fetus with periumbilical transfusions of immunologically compatible platelets (maternal platelets can be used) or maternal infusions of IgG and/or corticosteroids is possible – but not without significant risks
- Genetic counselling, identification of the paternal genotype (heterozygous for HPA-1 results in a 50% chance of a positive genotype fetus) and close liaison of the haematologist, obstetrician and neonatologist are essential.

### 8.3 Neonatal isoimmune thrombocytopenia

- Occurs in babies born to mothers with active or previous ITP
- Clinically identical presentation to ANT but treatment is different, in that maternal platelets cannot be used because they would be consumed
- Maternal steroid therapy before delivery may improve the fetal platelet count

### Drug-induced thrombocytopenia

An immune thrombocytopenia may occur with the following commonly prescribed drugs:

- Sodium valproate
- Phenytoin
- Carbamazepine
- Co-trimoxazole
- Rifampicin
- Heparin (non-immune mechanisms also possible)

### 8.4 Functional abnormalities of platelets

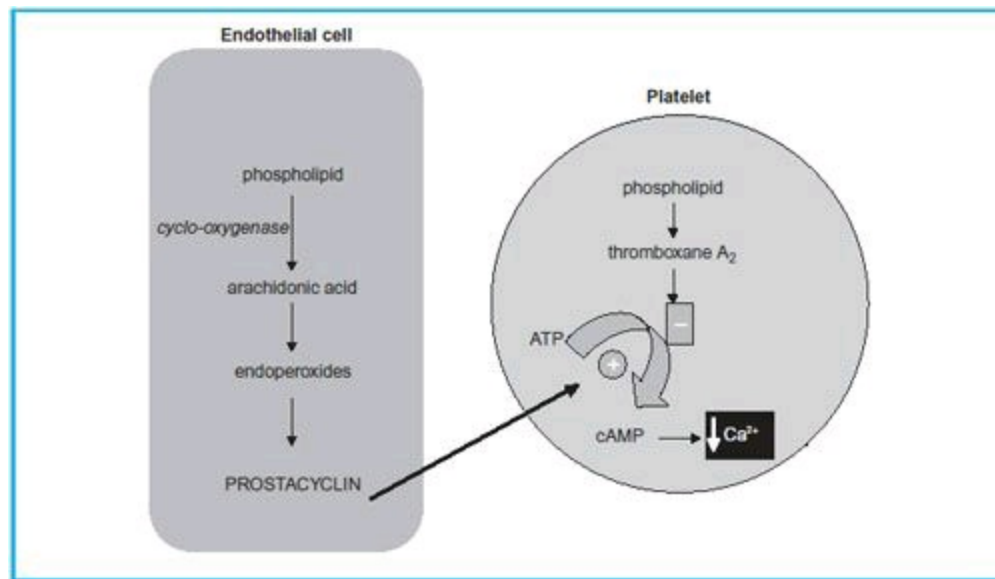
Before classifying these abnormalities it is important to understand the normal function of platelets. To achieve haemostasis, platelets undergo the following reactions of adhesion, secretion or release reaction, aggregation and procoagulation.

#### Adhesion

Adhesion of platelets to the subendothelial lining requires interactions between platelet membrane glycoproteins, elements of the vessel wall (e.g. collagen) and adhesive proteins such as von Willebrand factor (vWF) and fibronectin.

## Release reaction

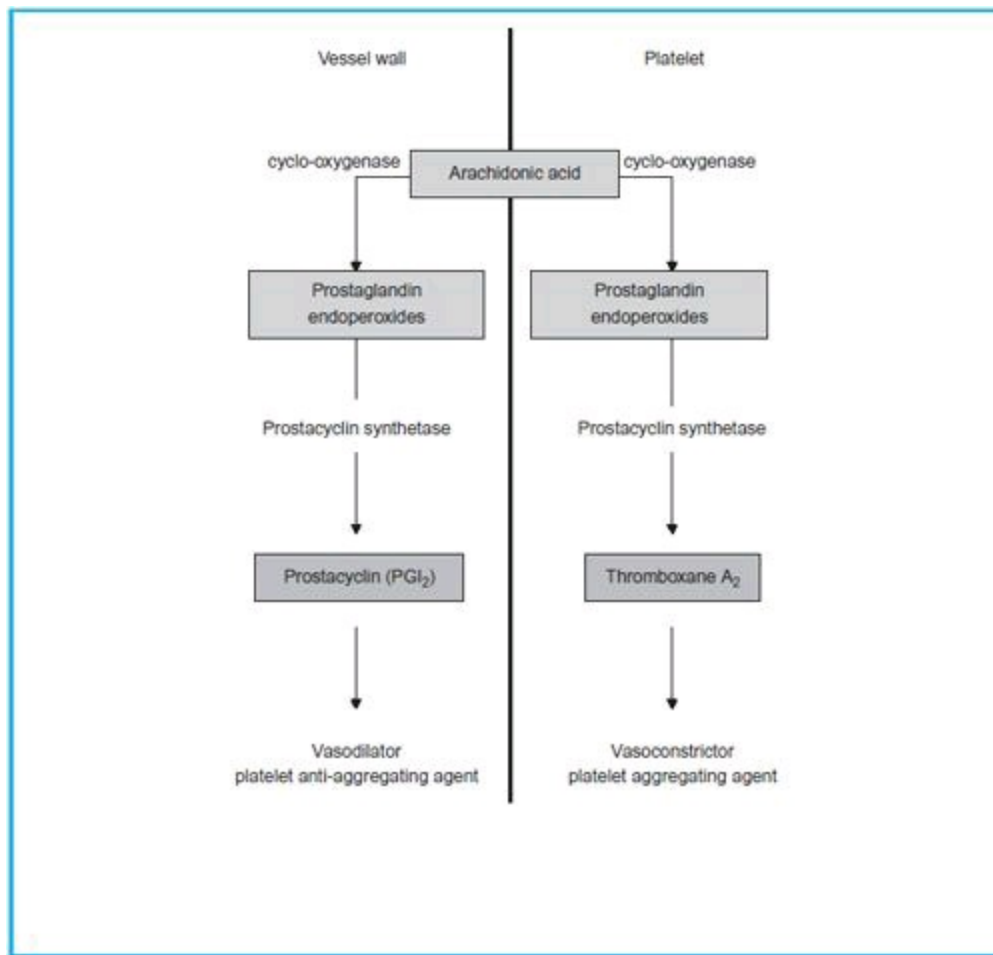
Collagen exposure results in the release or secretion of the contents of platelet granules: fibrinogen, serotonin, ADP, lysosomal enzymes, heparin-neutralizing factor. The cell membrane releases an arachidonate derivative that transforms into thromboxane  $A_2$  – a stimulus for aggregation as well as being a powerful vasoconstrictor.



Production of prostacyclin and thromboxane.

## Aggregation

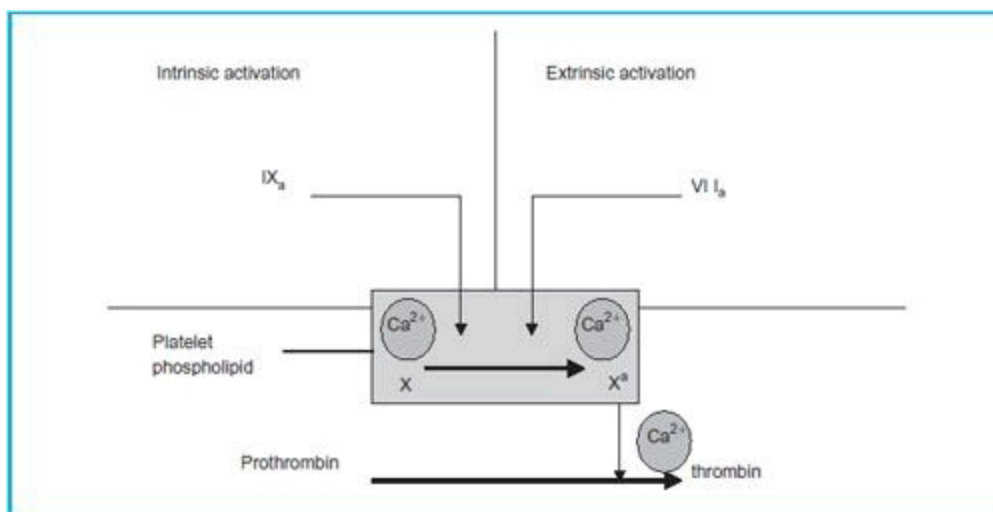
The contents of the platelet granules, specifically ADP and thromboxane  $A_2$ , cause additional platelets to aggregate at the site of the injury.



Function of prostacyclin and thromboxane.

## Platelet procoagulation activity

After secretion and aggregation have taken place a phospholipid (platelet factor 3) becomes exposed on the platelet membrane, thereby making itself available for its surface to be used as a template for two important coagulation protein reactions – the conversion of factor X to Xa and prothrombin to thrombin. These reactions are  $\text{Ca}^{2+}$  dependent.



Procoagulant activity.

## Functional platelet abnormalities – classification

# **Congenital**

## **Defects of platelet membrane**

- Glanzmann thrombasthenia: rare, autosomal recessive, failure to aggregate, normal platelet count and morphology
- Bernard–Soulier syndrome: rare, autosomal recessive, failure of adhesion, no receptor to bind to vWF, giant platelets, moderate platelet count reduction

## **Deficiency of storage granules**

- Wiskott–Aldrich syndrome
- Chédiak–Higashi syndrome

## **Defects of thromboxane deficiency**

- For example, thromboxane synthetase deficiency – cyclooxygenase deficiency

## **Acquired**

- Renal failure
- Liver failure
- Myeloproliferative disorders
- Acute leukaemia, especially myeloid
- Chronic hypoglycaemia
- Drugs
- Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), penicillin, cephalosporin, sodium valproate

## **Investigations**

- A prolonged bleeding time and normal or moderately reduced platelet count are the characteristic hallmarks of a congenital/hereditary platelet disorder (or von Willebrand disease)
- Platelet size followed by tests of aggregation and secretion in response to ADP, collagen, arachidonate and ristocetin will be necessary

## **9. BLOOD FILM**

### **9.1 Approach to a blood film at MRCPCH level**

#### **Is the pathology in the red or white blood cell?**

This is the first and most vital question that you need to ask yourself when presented with a blood

film to interpret. Apart from the accompanying history being important in helping you to answer this question, the other clue will be the number of white cells seen. If there is an abundance of white cells the likelihood that the pathology will be in the white cells is very high, with acute lymphoblastic leukaemia being top of your differential diagnosis. If only an occasional white cell is seen then red cell pathology is likely. Platelet pathology will be unlikely at MRCPCH level – the only real possibility is one of giant platelets (same size as a red cell, or bigger) in Bernard–Soulier syndrome.

## Red cell pathology?

Once you have decided on red cell pathology then look at the following parameters.

### Shape

- Sickle-shaped cells, as in sickle cell disease
- Fragments of red cells (e.g. helmet cells, etc.) indicative of microangiopathic haemolysis such as in the haemolytic–uraemic syndrome
- All different shapes, i.e. poikilocytosis as in thalassaemia, sickle cell disease, iron deficiency anaemia

### Size

- Small cells or microcytosis in iron deficiency anaemia
- Large cells or macrocytosis in vitamin B<sub>12</sub> and/or folate-deficient anaemia
- Different sizes: anisocytosis (haemoglobinopathies, anaemias)

### Amount of central pallor in red cell

- No central pallor: spherocytosis (e.g. hereditary spherocytosis, haemolytic conditions, burns)
- Large central pallor: hypochromic anaemia
- ‘Halo’ central pallor: target cells (haemoglobinopathies, hyposplenism)

### Red cell inclusions

- Malaria: most commonly *Plasmodium falciparum*, seen as a ‘signet-ring’ inclusion
- Howell–Jolly bodies: remnants of nuclear fragments, seen in hyposplenism
- Heinz bodies: denatured haemoglobin, resulting from oxidant stress (e.g. G6PD) or haemolysis; can be seen only with a special stain, so if normal staining was used then it is most likely a Howell–Jolly body
- Basophilic stippling: multiple small inclusions in a red cell, e.g. lead poisoning

## White cell pathology?

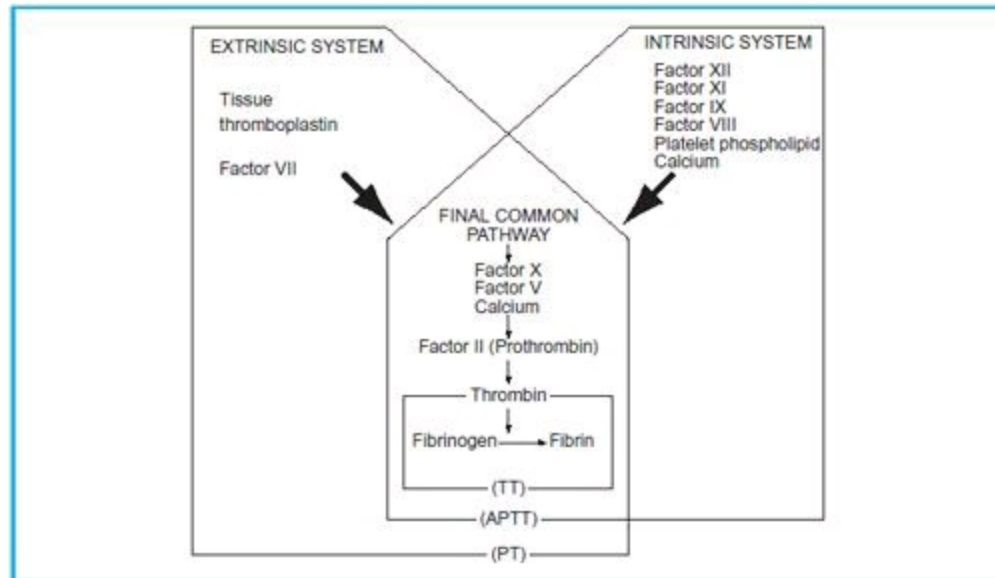
The abundance of white cells is most likely to be leukaemia at the MRCPCH level. A lymphoblast cell is recognized by its size (large), with a large nucleus taking up nearly the entire cell with only a rim of cytoplasm remaining (in contrast, a mature neutrophil has a multilobed small nucleus). The



morphological differentiation between acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) is not realistic at this level, but remember the relative incidence of each, 4:1, respectively.

## 10. COAGULATION

A representation of the coagulation cascades is shown below. It consists of an extrinsic pathway (tissue thromboplastin is the initiator) and the intrinsic pathway (what happens in the blood when it clots away from the body). These two pathways share a common final pathway resulting in the production of a fibrin clot.



Representation of the coagulation cascades.

The system can be divided into boxes, each box representing one of the following three basic screening tests of coagulation:

- **Prothrombin time (PT)** measures the extrinsic system and common pathway
- **Activated partial thromboplastin time (APTT)** measures the intrinsic system and common pathway
- **Thrombin time (TT)** measures the final part of the common pathway, it is prolonged by the lack of fibrinogen and by inhibitors of this conversion, e.g. heparin and fibrin degradation products

### 10.1 Natural anticoagulants

It is important that thrombin is limited to the site of injury. This is achieved by circulating inhibitors of coagulation:

- Antithrombin III – the most potent inhibitor, heparin potentiates its effect markedly
- Protein C inhibits factors Va and VIIIa and promotes fibrinolysis
- The action of protein C is enhanced by protein S

## 10.2 Coagulation disorders

### **Haemophilia A (factor VIII deficiency or absence)**

- Levels of factor VIII in carriers are variable because of random inactivation of the X chromosome (lyonization). As a result, DNA probes are now recommended to detect carrier status
- Prolonged APTT and factor VIII clotting assay reduced
- Bleeding time and prothrombin times are normal
- Vasopressin (DDAVP) may be useful in releasing endogenous factor VIII from its stores in mild haemophilia. Tranexamic acid, by inhibiting fibrinolysis, may be useful

### **Haemophilia B (factor IX deficiency or absence), Christmas disease**

- Exactly the same as above, except factor IX is involved rather than factor VIII
- Incidence is one-fifth that of haemophilia A

### **Von Willebrand disease**

Von Willebrand disease (vWD) is a more complicated entity compared with haemophilia A or B and is generally poorly described – hence it is often overlooked in clinical practice. It therefore deserves an in-depth explanation.

Von Willebrand factor is an adhesive glycoprotein encoded by a gene on chromosome 12. It is produced by endothelial cells and by platelets; vWF has two main functions:

- To stabilize and protect circulating factor VIII from proteolytic enzymes
- To mediate platelet adhesion

vWD will therefore result when the synthesis of vWF is reduced or when abnormal vWF is produced.

The clinical presentation of vWD will include the following:

- Mucous membrane bleeding
- Excess bleeding following surgical/dental procedures
- Easy bruising

Three types (at least) have been described.

#### **Type 1 vWD**

- Most common, accounts for at least 70% of vWD
- Due to a partial deficiency of vWF
- Autosomal dominant

## Type 2 vWD

- Due to abnormal function of vWF

## Type 3 vWD

- Due to the complete absence of vWF

Can often be mistaken for haemophilia A because factor VIII levels will be low as there is no vWF to protect factor VIII from proteolysis. Laboratory results are important in distinguishing the types of vWD and in the differentiation from haemophilia. In vWD type 1 the following results will be expected:

• Platelet count	N
• Bleeding time	N/↑
• Factor VIII	↓
• vWF	↓
• Ristocetin cofactor activity	↓

Ristocetin, an antibiotic, is now confined to laboratory-only use after it was documented to cause significant thrombocytopenia. Ristocetin, when added to a patient's plasma, will bind vWF and platelets together causing platelet aggregation (hence the clinical thrombocytopenia). In the absence of vWF, no platelet aggregation will be seen (vWF type 3). In the presence of decreased vWF, diminished aggregation will ensue (vWD type 1). Hence, when faced with the clinical picture of haemophilia A (bruising, normal platelet count, slightly increased bleeding time and a decreased factor VIII), the ristocetin cofactor test will be able to differentiate between vWD (decreased) and haemophilia A (normal).

## Vitamin K deficiency bleeding (VKDB) of early infancy

- Previously termed 'haemorrhagic disease of the newborn'.
- Classified into three categories depending on time of presentation:
  - Early – within first 24 h of delivery (usually associated with maternal drugs interfering with vitamin K metabolism, e.g. warfarin, anticonvulsants)
  - Classic – between 1 and 7 days (mainly idiopathic or in breastfed babies)
  - Late – day 8 onwards (usually peaks between 3 and 8 weeks), and can be idiopathic or secondary (e.g. malabsorption, cholestasis, antibiotic therapy, diarrhoea, breastfeeding)
- Bleeding can be from any site
- Vitamin K-dependent factors (factor II, VII, IX, X) are low at birth and fall further in breastfed infants in the first few days of life
- Other factors associated with this deficiency include:
  - Liver cell immaturity
  - Lack of gut bacterial synthesis of the vitamin K
  - Low quantities in breast milk (standard formula feeds contain 50 times the concentration of

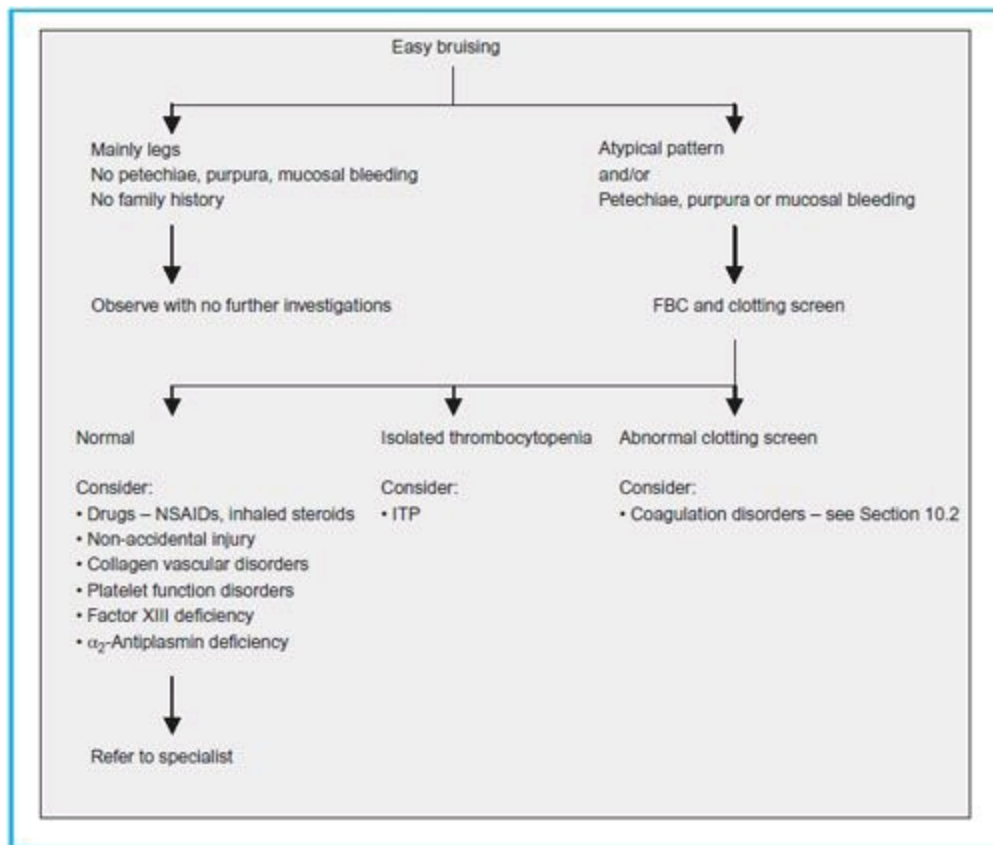
vitamin K compared with breast milk)

- PT is prolonged, APTT may be prolonged whereas platelet count and fibrinogen levels are normal. PT becomes prolonged only when prothrombin levels drop below about 50% of normal, so PT will detect only overt and not subclinical cases of VKDB. When vitamin K supply is limited, vitamin K-dependent coagulation factors produced will be defective (undercarboxylated). Such undercarboxylated factors (also known as ‘proteins induced by vitamin K absence or PIVKA’) can now be assayed, with the most readily available one being PIVKA-II. Now for the first time, subclinical vitamin K deficiency can be detected
- Treatment is with vitamin K<sub>1</sub> (phyloquinone) – single intravenous dose (250–300 µg/kg). If no intravenous access is possible, an intramuscular route must not be used because of possible bleeding complications; however, the subcutaneous route can be used
- Vitamin K restores the production of coagulation factors rapidly, with clinical effect seen within 20 min
- There is no international consensus on the best route of administration of prophylactic vitamin K to newborn babies. Many countries still utilize the gold standard of intramuscular administration whereas other countries give oral vitamin K
- There is no convincing evidence associating vitamin K administration and the risk of subsequent cancer, despite a UK-based possible association reported in the early 1990s. The American Academy of Pediatrics claims that there is no such evidence

## 11. BRUISING

### 11.1 An approach to easy bruising in children

Easy bruising in childhood is a common sign but poses significant challenge to the paediatrician regarding the level of investigation required, if any, and the responsibility of considering the possibility of non-accidental injury. Here is a simple approach to easy bruising:



An approach to easy bruising. (Modified from Voray A, Makris M. *Arch Dis Child* 2001;**84**:488491 [see Section 13].)

## 12. MALIGNANT PATHOLOGY

- There are 1200 new cases of malignancy diagnosed each year in the UK in children aged <15 years (an incidence of 1 in 600 children aged <15 years)
- The relative incidence rates for the different tumour types are illustrated below
- Leukaemia, together with lymphoma, accounts for almost 50% of all cases
- Brain and spinal cord tumours are the most commonly occurring solid tumours
- Overall, childhood cancer is about a third more common in boys than in girls

### Environmental factors predisposing to cancer

- Ultraviolet radiation – skin cancer, particularly malignant melanoma
- Ionizing radiation:
  - Preconceptual paternal exposure – remains controversial
  - In vitro exposure – increased incidence of leukaemia
  - Postnatal exposure – leukaemia
- Electromagnetic fields – remains controversial

### Syndromes/conditions predisposing to cancer

**Syndrome**

Down

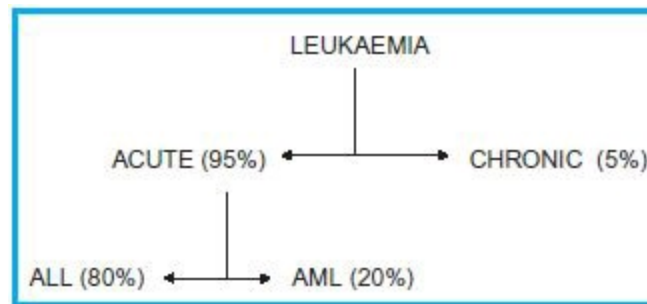
**Cancer**

Acute leukaemia

	20 times more susceptible than population
Neurofibromatosis type 1	Brain tumours, including optic glioma
	Juvenile myelomonocytic leukaemia
Li–Fraumeni	Phaeochromocytoma
	Soft tissue sarcomas
Gorlin	Brain tumours
	Medulloblastoma
	Basal cell carcinoma
Klinefelter	Germ-cell tumours, including dysgerminoma
Tuberous sclerosis	Benign tumours in organs
von Hippel–Lindau disease	Cerebellar haemangioblastomas – multiple
	Retinal angiomas
	Renal-cell carcinoma
	Phaeochromocytoma
Familial adenomatous polyposis (FAP)	Hepatoblastoma
	Thyroid cancer
	Medulloblastoma
WAGR	Wilms tumour
(Wilms tumour, aniridia, genitourinary abnormalities, learning disability)	
Beckwith–Wiedemann	Wilms tumour
(macroglossia, organomegaly, omphalos, hemihypertrophy)	Hepatoblastoma
	Rhabdomyosarcoma
	Neuroblastoma
	Adrenocortical carcinoma
Denys–Drash	Wilms tumour
(pseudohermaphroditism, Wilms tumour, nephrotic syndrome)	
Perlman	Wilms tumour
(phenotypically similar to Beckwith–Wiedemann)	
Xeroderma pigmentosum	Basal- and squamous-cell skin carcinoma
Ataxia telangiectasia	Leukaemia and B-cell lymphoma

## 12.1 Leukaemia

The leukaemias can be divided into acute and chronic leukaemia. Chronic leukaemia accounts for less than 5% of all leukaemias in childhood – all of these cases would be chronic myeloid leukaemia (CML) because chronic lymphoblastic leukaemia does not exist in childhood.



- In acute leukaemia, a differentiating white cell undergoes a structural and/or numerical change in its genetic make-up, causing a failure of further differentiation, dysregulated proliferation and clonal expansion
- Aetiology remains unknown, although associations or risk factors have been identified
  - Chromosomal breakage or defective DNA repair mechanisms (e.g. Fanconi anaemia, ataxia telangiectasia)
  - Chemotherapy – second malignancy effect
  - Immunodeficiency syndrome, e.g. Wiskott–Aldrich syndrome
  - Trisomy 21
  - Identical twin, especially if twin contracted leukaemia in infancy
  - Ionizing radiation
- Clinical presentation is related to bone marrow failure and possibly to extramedullary involvement

### Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is divided into B-cell or T-cell ALL depending on which cell line (determined by immunophenotyping) is affected. The majority of cases (>80%) originate from the B-cell line with pre-B, or common ALL (cALL), being the most common. About 15% are T-cell ALL with 2% demonstrating mixed lineage; cALL has the most favourable prognosis out of all the immunophenotypes.

Poor prognostic signs in ALL include:

- Presenting white cell count (WCC)  $>50 \times 10^9/l$
- $<2$  and  $>9$  years
- Boys do less well than girls
- Chromosomal abnormalities/translocations: rearrangement of the mixed lineage leukaemia (*MLL*) gene (11q23), e.g. t(4:11) purports a poor prognosis, whereas t(9:22) involving the Philadelphia chromosome carries a dismal prognosis
- Hypodiploidy (ploidy = number of chromosomes in lymphoblast). Near haploploidy carries the

worst prognosis and generally, as the ploidy increases, so does the prognosis, with hyperdiploidy the best

- African–Caribbean ethnicity
- CNS disease

The poor risk or prognostic factors above, together with the presence or absence of minimal residual disease (MRD) after induction treatment, are now used to tailor treatment, i.e. a child with a high WCC will receive more intensive treatment than if the WCC had been normal, patients with MRD-positive disease at various time points (predominantly at end of induction) will receive more intensive treatment. MRD detection (detection of lymphoblast clone by the use of polymerase chain reaction [PCR] or reverse transcription PCR [rt-PCR]) and associated prognostic significance has been one of the most important developments in the management of ALL over the last decade. Treatment is divided into three broad stages: induction, consolidation (including CNS-directed treatment) and maintenance, administered over a total period of 2.5–3 years. Cytotoxic/chemotherapy agents used in the treatment of leukaemia include the following: corticosteroids (prednisone and/or dexamethasone, vincristine, asparaginase, daunorubicin/doxorubicin, cytarabine, cyclophosphamide, methotrexate, mercaptopurine. CNS-directed treatment is a vital component of treatment because lymphoblasts can be protected from systemic chemotherapy by the blood–brain barrier. In standard-risk children this will comprise intrathecal chemotherapy at regular intervals, but for higher-risk children, high-dose intravenous methotrexate (at a sufficient dose to cross the blood–brain barrier) or cranial or cranio-spinal radiotherapy (very rarely used now) may be required. The long-term consequences of cranio-spinal/cranial radiotherapy are significant, and hence not commonly utilized now. Bone marrow transplantation is generally reserved for specific patients with relapsing ALL or with extremely poor prognosis ALL. The 5-year survival rate for standard-risk ALL is now in excess of 80%.

## **Acute myeloid leukaemia**

- AML is a heterogeneous group of haematological malignancies involving the precursors of the myeloid, monocyte, erythroid and megakaryocyte cell lines, in contrast to ALL, which involves the lymphoid cell line only
- AML is divided into seven subtypes depending on morphology (FAB – French, American, British classification) and immunophenotyping characteristics – M1–M7
- Chromosomal abnormalities occur in at least 80% of cases, with translocations the most common
- Treatment is with a more intensive, but shorter (6-month) chemotherapy regimen than that used for ALL
- Bone marrow transplantation plays a much more prominent role in the treatment of AML although its use remains controversial in some subsets of patients because the increased complete remission rates with this modality need to be weighed up against the increased mortality of the transplantation procedure
- Five-year survival figures are now in excess of 50%

The immediate dangers, at presentation, of patients with acute leukaemia, include: life-threatening infections, hyperleukocytosis/hyperviscosity syndrome, tumour lysis syndrome, bleeding and, in patients with an associated mediastinal mass, airway obstruction and ventricular outflow tract



obstruction may ensue. Prompt and careful attention to these potential complications are required.

## 12.2 Lymphoma

Two types of lymphoma are recognized: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). In NHL the originating cell is either a B or T lymphocyte, or an immature form thereof, whereas in HL the originating cell is a B-lineage lymphoid cell. Histologically, the presence of the Reed–Sternberg cell remains pathognomonic of HL.

### Non-Hodgkin lymphoma

- NHL is the term adopted to describe a heterogeneous group of malignant proliferations of lymphoid tissue
- The classification of NHL is complicated, and controversial. A practical way of classifying NHL is to divide the entities into immature forms (T- or B-cell acute lymphoblastic lymphoma), mature form (e.g. Burkitt lymphoma – a mature B-cell NHL) and large cell lymphomas (e.g. anaplastic large cell lymphoma, diffuse B-cell large cell lymphoma, peripheral T-cell lymphoma)
- The acute lymphoblastic lymphoma form of NHL is derived from the same T- and B-lineage lymphoid cells as ALL, but an important difference exists between these two entities. In ALL, 80% of cases are pre-B-cell derived, whereas 20% are T-cell derived. In NHL this is reversed, with T-cell tumours predominating

The following sites are commonly affected, in descending order of frequency:

- Abdomen – usually with B-cell disease
- Mediastinum – typically T cell in origin
- Head and neck – no specific cell

Chemotherapy is the mainstay of treatment because NHL is a systemic disease, despite the apparent local sites of disease.

### Hodgkin's lymphoma

- Painless cervical lymphadenopathy is the most frequent presenting symptom
- The EBV-related causal hypothesis remains unproven
- An excision biopsy of the entire lymph node, not just a biopsy of a portion of the node, is necessary to examine lymph node architecture and stromal cellular elements
- Presence of systemic symptoms (also known as 'B' symptoms: loss of weight, fever, night sweats) is negatively prognostic and therefore upstages patients to receive more intensive treatment
- Combined modality treatment with chemotherapy and radiotherapy remains the treatment of choice with attempts now being made to decrease treatment intensity (specifically radiotherapy) in an attempt to minimize treatment-related side effects. Patients with HL have the highest incidence of such complications compared with children with any other type of malignancy.
- Positron emission tomography (PET) scan is currently the focus of an international collaborative

trial to prospectively study the role of such metabolic imaging to help the decision of whether or not to safely withhold radiotherapy in patients depending on their PET scan response after two cycles of chemotherapy

### 12.3 Tumour-lysis syndrome

- High-count ALL (especially T-cell) and B-cell NHL (specifically Burkitt lymphoma) have the potential for bulky disease – a high cell mass, which will undergo lysis with treatment, resulting in the intracellular contents of potassium, phosphate and nuclear debris being released into the circulation
- Lymphoblast cells have four times the amount of phosphate compared to normal white cells
- Uric acid crystals and phosphate (precipitating out with calcium) crystals may cause acute renal failure and the following:
  - Fluid overload ↑
  - Phosphate ↑
  - Potassium ↑
  - Urea and creatinine ↑
  - Calcium ↓

Treatment involves:

- Hyperhydration
- Uric acid-lowering agents – urate oxidase (drug of choice) or allopurinol
- Treatment of hyperkalaemia
- Consideration of fluid filtration or dialysis

### 12.4 Tumours of the CNS

- The anatomical grouping together of brain tumours masks their diverse biological differences
- Brain tumours in children tend to be located in the posterior fossa, in the midline, have greater differentiation and have slightly better survival figures than their counterparts in adults
- Brain tumours as a general rule do not metastasize out of the CNS
- They are notoriously difficult to diagnose because of their varied and often non-specific presentations. The mean time from onset of symptoms to diagnosis is 5 months.

### Presenting symptoms of brain tumours

Presenting symptoms	Percentage of children
Vomiting	65
Headache	64
Changes in personality and mood	47

Squint	24
Out-of-character behaviour	22
Deterioration of school performance	21
Growth failure	20
Weight loss	16
Seizures	16
Developmental delay	16
Disturbance of speech	11

---

## **Astrocytoma**

- Most commonly occurring brain tumour
- Range from low-grade (benign) tumours, usually in the cerebellum, to high-grade (malignant) tumours, usually supratentorial and brain stem
- The high grade glioblastoma multiforme tumour has a near-fatal prognosis

## **Medulloblastoma (primitive neuroectodermal tumour (PNET) occurring in the cerebellum)**

- 20% of brain tumours
- The most commonly occurring high-grade tumour
- Recently it has become possible to classify medulloblastoma relative to the histology/biology of the tumour, with desmoplastic nodular subtype having the most favourable outcome and large cell medulloblastoma the least favourable
- Commonly metastasizes within the CNS, and it is the one tumour that may metastasize out of the CNS (<5% of cases)
- Prognosis is in the region of a 50–70% 5-year survival rate for standard-risk medulloblastoma

## **Brain-stem glioma**

- 20% of brain tumours
- Can be either diffuse (e.g. diffuse pontine glioma) or local
- Less than 10% survival

## **Craniopharyngioma**

- 8% of all brain tumours
- Situated in the suprasellar region predominantly
- Presenting features may be in the form of raised intracranial pressure, visual disturbances, pituitary dysfunction and psychological abnormalities

Treatment remains controversial but usually involves conservative surgery and/or radiotherapy

## 12.5 Retinoblastoma

Retinoblastoma usually presents with leukocoria (white eye reflex), strabismus or decreased vision. Retinoblastoma can be hereditary or sporadic.

### Hereditary

- 40% of retinoblastomas
- Deletion of a tumour-suppressor gene at chromosome 13q14
- Behaves in an autosomal dominant fashion (with a high degree of penetrance) but requires inactivation of remaining allele at the cellular level
- Usually presents with bilateral, and in some cases multifocal, disease
- Early onset (mean 10 months)
- Increased risk of developing a second primary tumour

### Sporadic

- 60% of retinoblastomas
- Unifocal
- Late onset (mean 18 months)

Treatment involves chemotherapy, focal treatment (cryotherapy, laser), enucleation, radiotherapy or combinations thereof, depending on the extent of tumour. It is a readily curable tumour if detected early with overall survival rate for unilateral retinoblastoma treated with enucleation alone being in excess of 95%.

## 12.6 Neuroblastoma

- Aggressive embryonal tumour of the autonomic system, originating from neural crest-derived sympathetic nerve cells (e.g. sympathetic chain, adrenal medulla)
- Most common cancer diagnosed at age <1 year
- Has the biological potential to involute and resolve spontaneously or behave aggressively with widespread metastases/organ invasion
- Presenting symptoms are extremely variable (asymptomatic to life-threatening invasive/metastatic disease) and can mimic commonly occurring conditions; symptoms are the result of the numerous possible tumour sites, metastases and the associated metabolic disturbances (caused by catecholamine secretion: sweating, pallor, diarrhoea, hypertension)
- Urinary and plasma catecholamine metabolites (vanillylmandelic acid [VMA]) and homovanillic acid [HVA]) may be raised

Prognostic factors are:

- Tumour stage: inversely proportional to outcome, with the exception of stage 4S – a local primary tumour with dissemination to liver, skin or bone marrow occurring in infancy in which spontaneous regression occurs in approximately 85% of patients
- Age: inversely proportional to outcome – patients <18 months have superior survival rates compared with older children.
- Histopathological characteristics, specifically the characteristics of the stroma
- Molecular biology: presence of the following confers a poor prognosis:
  - N-*myc* amplification
  - 11q abnormality
  - DNA ploidy – diploid worse than hypo-/hyperdiploid

Combining the above factors, four categories of neuroblastoma have been devised that will guide the intensity of treatment relative to the associated prognosis: very-low-, low-, intermediate- and high-risk groups. Treatment options range from observation only to the most intensive incorporating high-dose chemotherapy and stem cell rescue, surgery, radiotherapy, immune-mediated therapy, biological agents and MIBG therapy. High-risk NBL continues to have a poor prognosis (<50% 5-year event free survival rate).

## 12.7 Wilms' tumour (nephroblastoma)



- Embryonic tumour of the developing kidney
- Presents in a well child with a painless (or minimal discomfort) abdominal mass, and/or haematuria and/or hypertension (independently or collectively)
- Patients with Beckwith–Wiedemann syndrome have an increased propensity for developing Wilms tumours
- Intensity of treatment is relative to the staging and histology of the tumour, incorporating surgery (usually nephrectomy), chemotherapy and radiotherapy if required
- Very good overall prognosis – in excess of 90% 5-year survival rate

## 12.8 Bone tumours

### Osteosarcoma

- Twice as common as Ewing sarcoma
- Predominantly in the metaphyses of long bones, 50% occurring the knee joint (distal femur, proximal tibia)
- Presentation, usually with pain and/or mass, peaks in teenage years, suggesting a relationship between rapid bone growth and tumour formation
- High proportion of patients develop lung metastases

### Ewing sarcoma

- Occurs more commonly in flat bones (e.g. pelvis, ribs, vertebra) than osteosarcoma, although long bones can be affected
- Can be extraosseous in rare cases

## 12.9 Soft-tissue sarcomas

These are a group of tumours derived from contractile, connective, adipose and vascular tissue.

**Rhabdomyosarcoma** is the most common of these, arising from cells destined to be striated muscle cells. Rhabdomyosarcomas can occur anywhere in the body, with the common sites being genitourinary (bladder, prostate), parameningeal and orbital. Presentation is relative to the site of origin.

## 12.10 Malignant germ-cell tumours

Tumours derived from germ cells (cells giving rise to gonadal tissue) can be gonadal (30%) or extragonadal (70%):

- Extragonadal sites are the sacrococcygeal region, retroperitoneum, mediastinum, neck and the pineal area of the brain
- As gonadal tissue can give rise to any cell type, tumours derived from such cells may express any cell line in any stage of differentiation. This gives rise to a range of tumours, from an undifferentiated embryonal carcinoma to a benign and fully differentiated mature teratoma
- Presenting features vary reflecting site of origin but typically when gonadal in nature may present with testicular swelling in males, pelvic pain as a direct result of tumour extension or secondary to ovarian torsion caused by the tumour. Occasionally endocrinology-related pathology with abnormal or precocious puberty may be present
- Serum markers  $\alpha$ -fetoprotein and  $\beta$ -human chorionic gonadotrophin are useful in diagnosing and monitoring disease state

## 12.11 Hepatoblastoma

- Hepatoblastoma, an embryonal tumour of the liver, occurs in an otherwise normal liver (compared with hepatocellular carcinoma) and generally presents in children under the age of 2 years
- Patients with Beckwith–Wiedemann syndrome or familial adenomatous polyposis have an increased incidence of hepatoblastoma
- There is evidence to suggest that low-birthweight babies are predisposed to hepatoblastoma
- Presentation is often with an asymptomatic abdominal mass/swelling detected by parents when bathing or dressing their child
- Treatment involves chemotherapy and surgery (partial liver resection or in some cases liver transplantation)
- Overall survival rate figures of 70–80% have been reported

## 12.12 Langerhans cell histiocytosis

- Langerhans cell histiocytosis (LCH) is a clonal accumulation and proliferation of abnormal bone marrow-derived Langerhans cells. These cells, functioning as potent antigen-presenting cells, together with lymphocytes, eosinophils and normal histiocytes form infiltrates, in various organs, causing inflammatory tissue damage responsible for the morbidity, and in some cases mortality, associated with this disease
- Any age group may be affected
- Patients can have localized disease (to skin, bone or lymph node) or multisystem disease (with spleen, lung, liver and bone marrow involvement carrying a worse prognosis)
- The disease course is unpredictable – varying from spontaneous regression to rapid progression and death or repeated recurrences
- Treatment is with a combination of corticosteroids, vinblastine, methotrexate and 6-mercaptopurine

## 12.13 Haemophagocytic lymphohistiocytosis

- Haemophagocytic lymphohistiocytosis (HLH) is a rare disease resulting from abnormal proliferation of histiocytes (macrophages) in tissues and organs, causing an uncontrolled and ineffective immune response, with an associated high fatality rate
- Classified into familial or secondary HLH
- **Familial HLH** is an autosomal recessive condition, with five genetic mutations identified to date, resulting in a defect in the natural killer (NK) cell and T-cell cytotoxic function. It is thought that this causes strong immunological activation of phagocytes and mediators of inflammation, resulting in multisystem pathology that may, if untreated, be fatal. Active treatment with corticosteroids and chemotherapy is required in the acute phase followed by definitive treatment with a bone marrow transplantation
- **Secondary HLH**, or its other commonly used term ‘macrophage-activating syndrome’, is not inherited but has a similar pathophysiological process usually precipitated by infection, rheumatological, immune deficiencies, malignant and metabolic disorders
- Typical findings of HLH are fever, hepatosplenomegaly, cytopenia, hypertriglyceridaemia, coagulopathy, hypofibrinogenaemia, elevated soluble CD25, liver dysfunction, elevated ferritin and neurological symptoms.

## 12.14 Role of bone marrow (haematopoietic stem cell) transplantation

Haematopoietic stem cell transplantation can be:

- Autologous– the patient receives his or her own stem cells
- Allogeneic – patient receives donated stem cells from a donor; matched related or unrelated donor

Haematopoietic stem cell transplantation is indicated in the following conditions:

- **Malignancy:**
  - to eradicate disease, e.g. high-risk leukaemia
  - to rescue bone marrow following high dose therapy, e.g. myeloablative therapy in many solid tumours such as neuroblastoma, brain tumours
- **Metabolic:** to replace a missing/defective enzyme, e.g. mucopolysaccharidosis
- **Immunodeficiency:** to correct an underlying immune deficiency, for e.g. severe combined immune deficiency
- **Bone marrow failure syndromes:** to reconstitute normal bone marrow activity, e.g. acquired aplastic anaemia, congenital Fanconi anaemia
- **Haemoglobinopathy:** to correct abnormal globin chain, e.g. sickle cell disease, thalassaemia

Stem cells can be obtained from the donor via a bone marrow harvest or via peripheral blood stem cell collection or from umbilical cord blood.

## 12.15 Principles of managing malignancy

The ultimate goal of oncological treatment is to cure the patient, i.e. to ensure that the patient is in life-long remission, while at the same time keeping treatment-related side effects to the minimum.

The first step in achieving this goal in patients with haematological malignancies, such as leukaemia, is to get the patient into remission. This is achieved with induction chemotherapy, usually over a 4-week period. To ensure that this remission is durable, further treatment in the form of consolidation, intensification and maintenance chemotherapy is required.

Patients with solid-tumour malignancies generally require sequential multimodal treatment. In some isolated cases surgical resection may be sufficient for cure (e.g. gonadal stage 1 germ cell tumours). Adjuvant treatment after surgery is usually with chemotherapy and/or radiotherapy. In some instances where initial surgery is not indicated, i.e. tumour is anatomically irresectable, initial biopsy is performed to confirm tumour type and then the patient starts neoadjuvant therapy, usually in the form of chemotherapy but in some cases with radiotherapy. The aim here is to reduce tumour bulk in an attempt to minimize treatment-related morbidity and to ensure complete tumour resection. Disease, chemotherapy and/or radiotherapy is started to reduce tumour bulk, thereby enabling resection at a later stage of treatment.

## 12.16 Palliative care

Despite the high rate of cure in childhood cancer patients, approaching 80% in developed countries, palliative care is an integral component of the management of any paediatric haematology/oncology unit. Paediatric palliative care is an emerging specialty, reflecting the specific needs of the child, compared with adults, with a life-threatening condition: developmental factors influence the child's understanding of illness and death; the ability to communicate and participate in decision-making; parents play a very active caring role and decision-makers; different physiology and pharmacokinetics; sibling needs; and the grief of parents tends to be severe, complicated and more



prolonged. It is believed that early introduction of the patient and the family to the palliative care team is beneficial in order to facilitate a trusting and familiar relationship before the child enters a terminal state. Such an early intervention may be facilitated by introducing the palliative team as the symptom control team, to help manage challenging symptoms such as pain or seizures, for example. This close multidisciplinary interaction of paediatric oncologist, palliative care team, the child and the parents/family is fundamental in managing the symptoms of the child effectively, and shepherding the child/parents/family through a very emotional journey.

## 12.17 Late effects of cancer treatment

### Chemotherapy

#### Second malignancies

Leukaemia and lymphoma are the two most likely secondary malignancies to occur – particularly AML with topoisomerase II inhibitors (e.g. etoposide), whereas alkylators (e.g. nitrogen mustard, cyclophosphamide) may cause either.

#### Cardiac

Cardiomyopathy, secondary to anthracycline chemotherapy (e.g. doxorubicin) in a cumulative dose-dependent linear relationship, is the most likely complication. This toxicity may be exacerbated by thoracic radiotherapy.

#### Reduced fertility or infertility

Diminished fertility/infertility potential with increasing cumulative doses of alkylating chemotherapy (e.g. procarbazine, ifosfamide, cyclophosphamide) is possible.

#### Pulmonary

Pulmonary fibrosis may result from bleomycin-containing chemotherapy regimens, e.g. germ cell tumour, Hodgkin lymphoma regimens.

#### Neurocognitive

The use of methotrexate is linked to potential and neurocognitive limitations.

#### Auditory

Ototoxicity may result from platinum-containing agents, e.g. *cis*-platinum and to a lesser extent carboplatinum, used commonly in the treatment of CNS and other solid tumours.

#### Renal

Decreased renal function as measured by the glomerular filtration rate (GFR) and/or renal tubulopathy may be caused by platinum-containing agents, methotrexate, ifosfamide.

### Radiotherapy

The developing child is extremely susceptible to the damaging effects of radiotherapy, particularly in

the following areas:

- Neurocognitive – especially in the younger child
- Endocrine abnormalities – particularly growth and hypothyroidism
- Second malignancies – particularly sarcomas and lymphoma
- Musculoskeletal atrophy
- Organ damage, e.g. cardiac, lung, gastrointestinal

### 13. FURTHER READING

Adams RJ, McKie VC, Hsu L, et al. (1998). Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* **339**:5–11.

Blanchette V, Bolton-Maggs P (2010). Childhood immune thrombocytopenic purpura: diagnosis and management. *Hematol Oncol Clin North Am* **24**:249–73.

Bussel J (2009). Diagnosis and management of the fetus and neonate with alloimmune thrombocytopenia. *J Thromb Haemost* **7**(suppl 1):253–7.

Di Bartolomeo P, Santarone S, Di Bartolomeo E, et al. (2008). Long-term results of survival in patients with thalassemia major treated with bone marrow transplantation. *Am J Hematol* **83**:528–30

Freeman HR, Ramanan AV (2011). Review of haemophagocytic lymphohistiocytosis. *Arch Dis Child* **96**:688–93.

Kontoghiorghe GJ (2011). The Proceedings of the 19th International Conference On Chelation, London, UK: major changes in iron chelation therapy in the last 25 years using deferiprone (L1) has resulted In the complete treatment of iron overload. *Hemoglobin* **35**:181–5.

Maris JM (2010). Recent advances in neuroblastoma. *N Engl J Med* **362**:2202–11

Neufeld EJ (2010). Update on iron chelators in thalassemia. *Hematol Am Soc Hematol Educ Program* 451–5.

Pui CH, Evans WE (2006). Treatment of acute lymphoblastic leukemia. *N Engl J Med* **354**:166–78.

Pui CH, Relling MV, Downing JR (2004). Acute lymphoblastic leukemia. *N Engl J Med* **350**:1535–48.

Rees DC, Williams TN, Gladwin MT (2010). Sickle cell disease. *Lancet* **376**:2018–31.

Segel GB, Feig SA (2009). Controversies in the diagnosis and management of childhood acute immune thrombocytopenic purpura. *Pediatr Blood Cancer* **53**:318–24.

Shearer MJ (2009). Vitamin K deficiency bleeding (VKDB) in early infancy. *Blood Rev* **23**:49–59.

Voray A, Makris M (2001). An approach to investigation of easy bruising. *Arch Dis Child* 84:488-491

Walters MC (2010). Gene therapy and bone marrow transplantation for thalassemia: changing of the guard? *Mol Ther* **18**:1577.

---

# Chapter 13

## Hepatology

*Nancy Tan and Anil Dhawan*

---

## CONTENTS

### **1. Jaundice in infancy**

- [1.1 Bilirubin metabolism](#)
- [1.2 Approach to a jaundiced infant](#)
- [1.3 Unconjugated hyperbilirubinaemia](#)
- [1.4 Conjugated hyperbilirubinaemia](#)

### **2. Acute hepatitis**

- [2.1 Acute infective hepatitis](#)
- [2.2 Drug-induced liver disease](#)

### **3. Acute liver failure**

- [3.1 Paracetamol poisoning](#)
- [3.2 Wilson disease](#)

### **4. Chronic liver disease and end-stage liver failure**

- [4.1 Autoimmune hepatitis](#)
- [4.2 Chronic viral hepatitis](#)
- [4.3 Non-alcoholic fatty liver disease](#)
- [4.4 Liver transplantation](#)

### **5. Portal hypertension**

### **6. Liver function test**

### **7. The pancreas**

- [7.1 Acute pancreatitis](#)

## [8. Further reading](#)

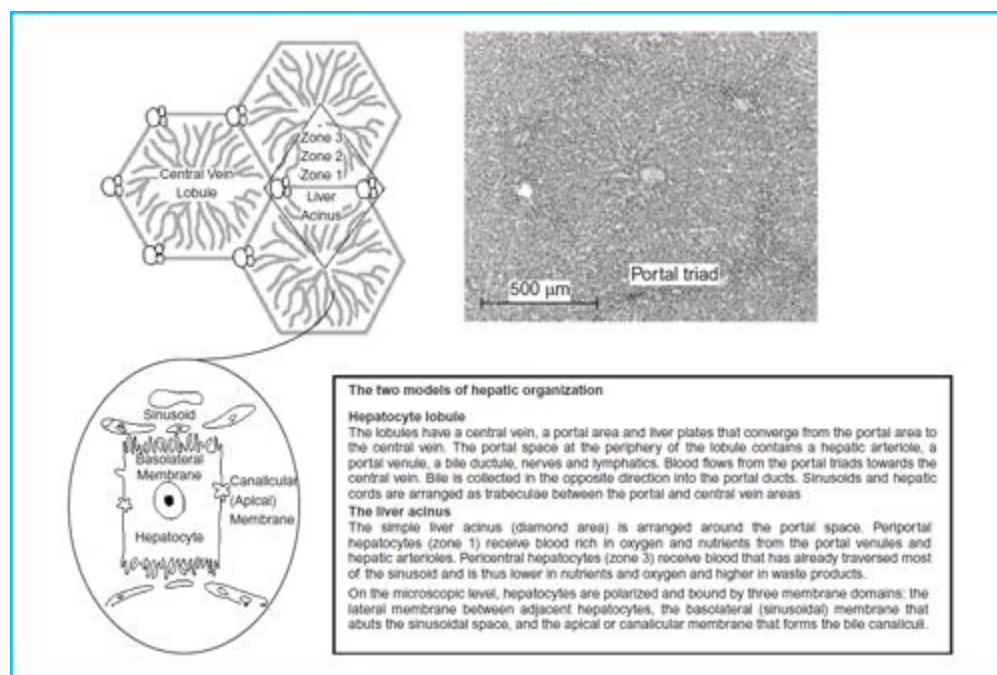
# Hepatology

## 1. JAUNDICE IN INFANCY

See also Chapter 16 – Neonatology, Section 10.

### 1.1 Bilirubin metabolism

- Unconjugated bilirubin is a product of haem metabolism and is transported by albumin to the hepatocytes
- Hepatocyte uptake is via membrane receptor carriers or by simple passive diffusion
- Conjugation with glucuronic acid by esterification to make it water soluble (enzyme – bilirubin uridine diphosphate glucuronosyltransferase – UGT)
- Secretion of conjugates against a concentration gradient through the canalicular membrane into the bile



The two models of hepatic organization

## 1.2 Approach to a jaundiced infant

- 30–50% of normal term neonates experience jaundice; *few have significant underlying disease*
- Physiological and breast-milk jaundice (unconjugated hyperbilirubinaemia) account for the majority of cases in the first weeks of life
- Approximately 1 in every 2500 infants is affected with cholestatic jaundice (conjugated hyperbilirubinaemia)
- Infants with risk factors should be monitored closely in the first days to weeks of life

### Factors that influence hyperbilirubinaemia

Identify babies as being more likely to develop significant hyperbilirubinaemia if they have any of the following:

- Gestational age <38 weeks
- A previous sibling with neonatal jaundice requiring phototherapy
- Mother's intention to breastfeed exclusively
- Visible jaundice in the first 24 hours of life

### Risk factors for kernicterus/or adverse sequelae

Identify babies with hyperbilirubinaemia as being at increased risk of developing kernicterus if they have any of the following:

- A serum bilirubin level >340  $\mu\text{mol/l}$  in babies with a gestational age  $\geq 37$  weeks
- A rapidly rising bilirubin level >8.5  $\mu\text{mol/l}$  per h
- Clinical features of acute bilirubin encephalopathy

Up to 15% of neonates can be jaundiced at 2 weeks of age and need to be investigated.

In babies with a gestational age  $\geq 37$  weeks with jaundice lasting more than 14 days, and in babies with a gestational age <37 weeks with jaundice lasting more than 21 days:

- Look for pale chalky stools and/or dark urine that stains the nappy
- Measure the conjugated bilirubin
- Carry out a full blood count
- Carry out a blood group determination (mother and baby) and DAT (Coombs test). Interpret the result taking account of the strength of reaction, and whether mother received prophylactic anti-D immunoglobulin during pregnancy:
- Carry out a urine culture
- Ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed

## 1.3 Unconjugated hyperbilirubinaemia

- The most common causes include:
  - Physiological jaundice
  - Breast-milk jaundice
  - Haemolysis
  - Congenital hyperbilirubinaemia
- Unconjugated bilirubin is normally tightly bound to albumin
- Kernicterus may result from high levels of unbound, lipid-soluble, unconjugated bilirubin
- Albumin-bound bilirubin may also cross the blood–brain barrier if damage has occurred because of asphyxia, acidosis, hypoxia, hypoperfusion, hyperosmolality or sepsis in the newborn
- Management strategy is with phototherapy, adequate hydration, and identification and treatment of the underlying causes

### Effects of bilirubin toxicity in the newborn baby

Early (3–4 days)	Late (>1 week)	Chronic (evident by 3 years)
Lethargy	Irritability	Athetoid cerebral palsy
Poor feeding	Opisthotonos	High-frequency hearing loss
High-pitched cry	Seizures	Paralysis of upward gaze
Hypotonia	Apnoea	Dental dysplasia
	Oculogyric crisis	Mild learning disability
	Hypertonia	
	Fever	

### Physiological jaundice

- 50% of term and 80% of preterm babies are jaundiced in the first week of life
- Jaundice within the first 24 h of life is **always** pathological and cannot be attributed to physiological jaundice
- The aetiology of physiological jaundice is not precisely known but may be related to immaturity of bilirubin UGT activity
- Jaundice peaks on day 3 of life; declines over first week
- Treatment is by phototherapy or by exchange transfusion for severe hyperbilirubinaemia

### Breast-milk jaundice

- Occurs in 0.5–2% of neonates
- Early onset: develops after day 4, relative caloric deprivation, decreased volume and frequency of feeding with resultant mild dehydration and delayed passage of meconium



- Late onset: develops around day 7, substances in maternal milk, such as  $\beta$ -glucuronidases, and non-esterified fatty acids, may inhibit normal bilirubin metabolism
- Jaundice peaks around the end of the second week
- May overlap with physiological jaundice or be protracted for 1–2 months
- Diagnosis is supported by a drop in serum bilirubin ( $\geq 50\%$  in 1–3 days) if breastfeeding is interrupted for 48 hours

## **Haemolysis**

- Commonly the result of isoimmune haemolysis (rhesus [Rh], ABO incompatibility), red cell membrane defects (congenital spherocytosis, hereditary elliptocytosis), enzyme defects (glucose-6-phosphate dehydrogenase or pyruvate kinase deficiency) or haemoglobinopathies (sickle cell anaemia, thalassaemia)
- Findings of jaundice in the presence of anaemia and a raised reticulocyte count would necessitate further investigation for the cause of haemolysis

## **Inherited disorders of unconjugated hyperbilirubinaemia**

This spectrum of disease depends on the degree of bilirubin UGT deficiency. Liver function tests and histology are normal.

### **Gilbert syndrome**

- Mild deficiency ( $\geq 50\%$  decrease of UGT activity) occurring in 7% of population
- Polymorphism with TA repeats in the promoter region (TATA box) in white individuals compared with exon mutations in Asian individuals on chromosome 2q37
- Correlation between hepatic enzyme activity and serum bilirubin levels is unpredictable because up to 40% of patients with Gilbert syndrome have a reduced red blood cell lifespan
- Higher incidence of neonatal jaundice and breast-milk jaundice
- Usually presents after puberty with an incidental finding of elevated bilirubin on blood tests or jaundice after a period of fasting or intercurrent illness
- More common in males
- No treatment required, compatible with normal lifespan

### **Crigler–Najjar type II**

- Moderate deficiency
- May require phototherapy and phenobarbital

### **Crigler–Najjar type I**

- Severe deficiency of UGT
- High risk of kernicterus
- Requires life-long phototherapy or even liver transplantation

Autosomal recessive inheritance. Both Gilbert syndrome and Crigler–Najjar type II can also have autosomal dominant transmission.

**Causes of neonatal unconjugated hyperbilirubinaemia**

**Increased production of unconjugated bilirubin from haem**

Haemolytic disease (hereditary or acquired)

- Isoimmune haemolysis (neonatal; acute or delayed transfusion reaction; autoimmune):
  - Rh incompatibility
  - ABO incompatibility
  - Other blood group incompatibilities
- Congenital spherocytosis
- Hereditary elliptocytosis
- Infantile pyknocytosis
- Erythrocyte enzyme defects:
  - Glucose-6-phosphate dehydrogenase deficiency
  - Pyruvate kinase deficiency
- Haemoglobinopathy:
  - Sickle cell anaemia
  - Thalassaemia
  - Others
- Sepsis
- Microangiopathy:
  - Haemolytic–uraemic syndrome
  - Haemangioma

Ineffective erythropoiesis

Drugs

Infection

Enclosed haematoma

Polycythaemia:

- Diabetic mother
- Fetal transfusion (recipient)
- Delayed cord clamping

**Decreased delivery of unconjugated bilirubin (in plasma) to hepatocyte**

Right-sided congestive heart failure

Portacaval shunt

**Decreased bilirubin uptake across hepatocyte membrane**

Presumed enzyme transporter deficiency

Competitive inhibition:

- Breast-milk jaundice
- Lucy–Driscoll syndrome
- Drug inhibition (radiocontrast material)

Miscellaneous:

- Hypothyroidism
- Hypoxia
- Acidosis

## **Decreased storage of unconjugated bilirubin in cytosol (decreased Y and Z proteins)**

Competitive inhibition

Fever

## **Decreased biotransformation (conjugation)**

Physiological jaundice

Inhibition (drugs)

Hereditary (Crigler–Najjar):

- Type I (complete enzyme deficiency)
- Type II (partial deficiency)

Gilbert disease

Hepatocellular dysfunction

## **Enterohepatic recirculation**

Intestinal obstruction:

- Ileal atresia
- Hirschsprung disease
- Cystic fibrosis
- Pyloric stenosis

Antibiotic administration

## **Breast-milk jaundice**

# **1.4 Conjugated hyperbilirubinaemia**

- Jaundice, dark urine, pale stools and hepatomegaly or hepatosplenomegaly
- Baby may be acutely ill with hypoglycaemia, acid–base imbalance, electrolyte imbalance, coagulopathy and liver failure
- Biochemical definition is direct bilirubin >20% of total
- Top causes are:
  - ‘Idiopathic’ neonatal hepatitis (40%)
  - Extrahepatic biliary atresia (25–30%)
  - Intrahepatic cholestasis syndromes (20%), e.g. Alagille syndrome, progressive familial intrahepatic cholestasis (PFIC)
  - $\alpha_1$ -Antitrypsin deficiency (7–10%)

## Work-up of conjugated hyperbilirubinaemia

Investigations	Pathology
<b>General investigations</b>	
Liver function tests	Type and level of jaundice Degree of liver failure Normal GGT levels (PFIC1, PFIC2 and defects of bile acid synthesis)
Full blood count and peripheral blood film	Marrow suppression (familial haemophagocytic lymphohistiocytosis, lysosomal storage diseases) Anaemia/acanthocytosis/thrombocytosis (HFI) Vacuolated lymphocytes (Wolman disease)
PT/PTT, INR	Coagulopathy (liver failure) Vitamin K deficiency
Blood glucose	Hypoglycaemia (liver failure, metabolic disorders)
Renal function test	Impaired renal function (liver failure, Zellweger syndrome)
Lipid profile	Hypercholesterolaemia and hypertriglyceridaemia (Wolman syndrome, Alagille syndrome, PFIC)
Blood gas	Metabolic acidosis (metabolic disorders)

**Infections**

Urine cultures	Urinary tract infection
Herpes, toxoplasma, CMV, rubella, syphilis, parvovirus B19 serology	Intrauterine infection
Hepatitis B and A serology HIV	Hepatitis B and rarely hepatitis A
Enterovirus serology, CSF for PCR or cultures	Neonatal systemic infection
Blood cultures, CSF cultures	Systemic bacterial infection

**Endocrine**

Thyroid function test	High TSH, low T <sub>4</sub> , free T <sub>4</sub> and T <sub>3</sub> (hypothyroidism, hypopituitarism)
Cortisol	Low cortisol (hypopituitarism, septo-optic dysplasia)

**Metabolic**

Serum $\alpha_1$ -antitrypsin levels and PI type	Low level and PI ZZ ( $\alpha_1$ -antitrypsin deficiency)
Galactose-1-phosphate uridyl transferase (Gal-1-PUT)	Deficiency (galactosaemia)
Lactate	Elevated (HFI, mitochondrial disorders)
Urine-reducing substances	Positive (galactosaemia, HFI)
Ferritin	Grossly elevated (neonatal haemochromatosis)
$\alpha$ -Fetoprotein	Grossly elevated (tyrosinaemia)
Plasma amino acid, urine amino acid	3 $\times$ $\uparrow$ plasma tyrosine, phenylalanine, methionine, $\uparrow$ urinary succinylacetone (tyrosinaemia)

Urinary organic acid	Organic aciduria (tyrosinaemia, peroxisomal enzyme deficiency, mitochondrial hepatopathies)
Urinary bile acid intermediates	Elevated (primary disorders of bile acid synthesis, Zellweger syndrome)
Very long chain fatty acids (VLCFA)	Elevated (peroxisomal enzyme deficiency)
Plasma transferrin isoforms	Characteristic patterns in congenital disorders of glycosylation
Sweat chloride	Abnormal chloride levels (cystic fibrosis, PFIC)
<b>Genetic testing</b>	
Karyotyping	Trisomy (trisomies 21 and 18) Duplication of chromosome 22 (cat eye syndrome)
Specific mutations	
<b>Immune</b>	
Autoantibodies	Anti-Ro and anti-La antibodies (neonatal lupus erythematosus)
<b>Biopsy</b>	
Liver	Biliary atresia Giant cell hepatitis Immunostaining for PFIC Bile duct paucity (syndromic and non- syndromic causes) Gaucher cells (Gaucher syndrome) Foamy histiocytes (Niemann–Pick, Wolman)
Lip	Extrahepatic siderosis (neonatal haematochromatosis)
Skin biopsy and fibroblast culture studies	Sea blue histiocytes (Wolman disease)

Accumulation of intracytoplasmic unesterified cholesterol (Niemann–Pick C)  
 Glucocerebrosidase deficiency (Gaucher)  
 Sphingomyelinase deficiency (Niemann–Pick A, B)  
 Acid lipase deficiency (Wolman)  
 $\alpha$ 1,4-glycan-6-glycosyltransferase deficiency (GSD IV)

Muscle biopsy      Steatosis and ragged red fibres, respiratory chain enzyme analysis (mitochondrial)

Bone marrow aspirate      Gaucher cells (Gaucher)  
    ‘Foam’ cells (Niemann–Pick, Wolman)  
    Erythrophagocytosis (familial phagocytic lymphohistiocytosis)

## Imaging

Hepatobiliary ultrasound      Adrenal calcification (Wolman)  
    Triangular cord sign and absent or small irregular gall bladder (biliary atresia)  
    Structural abnormalities (e.g. choledochal cyst)

HIDA scan      Normal excretion excludes biliary atresia.  
                                  Delayed or no excretion usually seen in neonatal hepatitis

**Eye examination**      Cherry red spot (Niemann–Pick)  
                                  ‘Oil-drop’ cataracts, intraocular haemorrhage and retinal detachment (galactosaemia)  
                                  Corneal clouding, cataracts, pigmentary retinopathy (Zellweger syndrome)  
                                  Coloboma (cat-eye syndrome)  
                                  Posterior embryotoxon, optic disc drusen (Alagille syndrome)

---

GGT,  $\gamma$ -glutamyl transferase; PT/PTT, prothrombin time/partial thromboplastin time; INR, international normalized ratio; CMV, cytomegalovirus; HIV, human immunodeficiency virus; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; TSH, thyroid-stimulating hormone; T<sub>3</sub>, triiodothyronine; HFI, hereditary fructose intolerance; T<sub>4</sub>, thyroxine; PI, protease inhibitor.

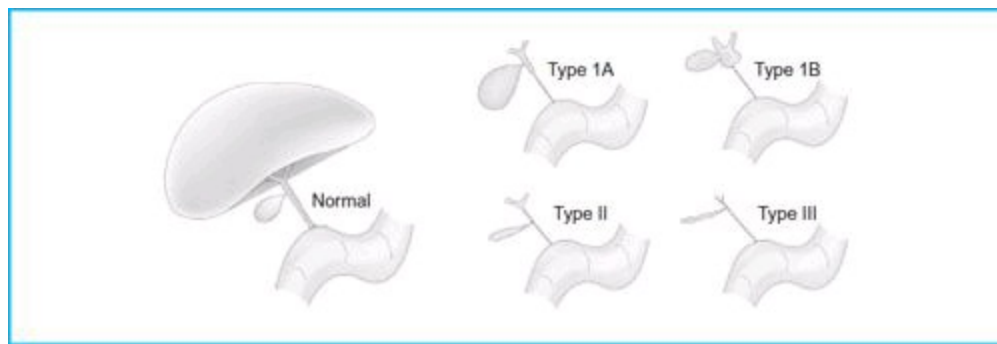
# Idiopathic neonatal hepatitis

- Diagnosis of exclusion
- Associated with low birthweight or prematurity
- Histology
  - Hepatocellular swelling (ballooning), focal hepatic necrosis and multinucleated giant cells
  - Bile duct proliferation and bile duct plugging are usually absent
- Factors predicting poor prognosis
  - Severe jaundice beyond 6 months
  - Acholic stools
  - Familial occurrence
  - Persistent hepatosplenomegaly
- 90% do well with no long-term liver disease

## Biliary atresia (BA)

- Incidence: 1 per 16 000 live births
- Slight female preponderance
- Exact pathogenesis is unknown
- 25% associated with other congenital malformations
- Anatomical variants:
  - Type I – obliteration of the common bile duct
  - Type II – obliteration is extended to the common hepatic duct
  - Type III – obliteration of the entire extrahepatic biliary tree (most common form)
- Diagnosis is suggested by:
  - Hepatobiliary ultrasound (*fasting*) – will show absent gallbladder or irregular outline and triangular cord sign
  - Radionuclide imaging (*phenobarbital priming*) – no excretion indicates possible biliary atresia; excretion indicates that it is not biliary atresia
  - Liver biopsy – expanded portal tracts with bile duct proliferation, bile plugs and fibrosis
  - Gold standard for diagnosis is exploratory and operative cholangiography
- Portoenterostomy (Kasai operation) should be offered to all children unless there is decompensated liver disease
- Between 70 and 80% achieve partial bile flow with 50% becoming jaundice free after surgery
- Ascending bacterial cholangitis follows the first year of surgery in 45–50%
- It is a progressive disease even with a successful Kasai operation, although prognosis may be better if procedure is performed within 8 weeks of birth
- Majority (80%) require liver transplantation by 20 years of age
- Fat-soluble vitamin supplementation is essential
- Role of choleretic agents such as phenobarbital and ursodeoxycholic acid and steroids is unproven





The three variants of biliary atresia

## Alagille syndrome (arteriohepatic dysplasia)

- Autosomal dominant
- Incidence is 1 per 100 000 live births
- Defect of the *JAG1* gene on chromosome 20p12
- Intrahepatic biliary hypoplasia
- Characteristic facies (may not be prominent at birth):
  - Broad forehead
  - Deep-set eyes
  - Mild hypertelorism
  - Small chin
- Skeletal abnormalities:
  - Thoracic hemivertebrae/‘butterfly’ vertebrae
- Eye findings:
  - Posterior embryotoxon
  - Retinal changes
- Cardiac disease:
  - Peripheral pulmonary artery stenosis
  - Other congenital cardiac malformations
- Intrauterine growth retardation and faltering growth with severe malnutrition occur in 50%
- Others:
  - Renal disease
  - Delayed puberty or hypogonadism
  - Learning disability, learning difficulties or psychosocial dysfunction
  - Vascular abnormalities
  - Hypothyroidism and pancreatic insufficiency
  - Recurrent otitis media, chest infection
  - Hypercholesterolaemia
- Variable phenotype; severe liver disease may require liver transplantation

## Progressive familial intrahepatic cholestasis

Group of inherited diseases which present as neonatal hepatitis, faltering growth, pruritis and progressive liver disease, requiring liver transplantation in the first few years of life.

### Type 1

- Byler disease
- Mutation of the *FIC1* gene on chromosome 18q21-22
- Pancreatitis, persistent diarrhoea, short stature and sensorineural hearing loss
- Normal  $\gamma$ -glutamyltransferase (GGT), serum cholesterol
- Elevated serum bile salts, sweat chloride
- Low chenodeoxycholic acid in bile

### Type 2

- Mutations on chromosome 2q24, bile salt export pump (*BSEP*) gene
- Normal GGT

### Type 3

- Mutations in the P-glycoprotein MDR-3 gene (*ABCB4*)
- Elevated GGT
- Bile phospholipids 15% of normal

## $\alpha_1$ -Antitrypsin deficiency

- Most common inherited cause of conjugated jaundice
- Autosomal recessive
- Incidence is 1 in 1600–2000 live births
- Mutation at the protease inhibitor (Pi) locus on chromosome 14
- More than 75 variants are known but not all mutations result in disease
- The most common disease phenotype is PiZZ, homozygous for a point mutation in which glutamic acid is replaced by glycine at position 342. This causes abnormal folding of the  $\alpha_1$ -antitrypsin molecule so that it becomes trapped in the endoplasmic reticulum, causing liver damage
- Associated with intrauterine growth retardation
- Hepatomegaly at presentation is common
- Cholestasis may be severe enough to produce totally acholic stools
- Approximately 2% of infants will present with vitamin K-responsive coagulopathy
- Diagnosis is from:
  - Low  $\alpha_1$ -antitrypsin levels
  - Phenotype (Pi) by isoelectric focusing
- Replacement with recombinant  $\alpha_1$ -antitrypsin is not helpful because abnormal protein continues to accumulate in the endoplasmic reticulum
- Prognosis – 50% of children presenting with neonatal hepatitis develop chronic liver disease with half of them requiring a liver transplantation in the first 10 years of life.

## Causes of conjugated jaundice

# Infections

## *Bacterial*

- Urinary tract infection
- Septicaemia<sup>7</sup>
- Syphilis
- Listeriosis
- Tuberculosis

## *Parasitic*

- Toxoplasmosis
- Malaria

## *Viral*

- Cytomegalovirus
- Herpes simplex virus<sup>7</sup>
- Human herpesvirus type 6<sup>7</sup>
- Herpes zoster virus
- Adenovirus
- Parvovirus<sup>7</sup>
- Enterovirus
- Reovirus type 3
- Human immunodeficiency virus
- Hepatitis B virus<sup>7</sup>
- ? Hepatitis A
- ? Rotavirus

# Metabolic disorders

## *Carbohydrate metabolism*

- Galactosaemia<sup>7</sup>
- Fructosaemia<sup>7</sup>
- Glycogen storage type 4
- Congenital disorders of glycosylation<sup>7</sup>

## *Protein metabolism (amino acid)*

- Tyrosinaemia<sup>7</sup>
- Hypermethioninaemia

- Urea cycle defects (arginase deficiency)

## ***Lipid metabolism***

- Niemann–Pick disease (type C)
- Wolman disease<sup>7</sup>
- Cholesterol ester storage disease

## ***Bile acid disorders***<sup>7</sup>

Fatty acid oxidation defects<sup>7</sup>

Disorders of oxidative phosphorylation<sup>7</sup>

Zellweger syndrome

Other mitochondrial disorders<sup>7</sup>

## **Endocrine disorders**

Hypothyroidism

Hypopituitarism (with or without septo-optic dysplasia)

## **Chromosomal disorders**

Down syndrome

Trisomy E

Patau syndrome

Leprechaunism

### **Other genetic–metabolic defects**

$\alpha_1$ -Antitrypsin deficiency

Cystic fibrosis

Familial cholestasis syndromes

- Alagille syndrome
- Byler syndrome (PFIC-1)
- Bile salt export protein defect (BSEP defect, PFIC-2)
- Multidrug-resistant 3 deficiency (MDR-3, PFIC-3)
- Hereditary cholestasis with lymphoedema (Aagenaes syndrome)

## **Metals and toxins**

Neonatal haemochromatosis<sup>7</sup>

Copper-related cholestasis<sup>7</sup>

Parenteral nutrition

Drugs

## Haematological disorders

Haemophagocytic lymphohistiocytosis<sup>7</sup>

Langerhans cell histiocytosis

Inspissated bile syndrome

## Biliary tree disorders

Biliary atresia

Mucus plug

Bile duct stenosis/stricture

Spontaneous perforation of common bile duct

Neonatal sclerosing cholangitis

Caroli disease

Compression of bile duct by a mass

Inflammatory pseudotumour at porta hepatis

## Immunological disorders

Neonatal lupus erythematosus

Giant cell hepatitis with Coombs test-positive haemolytic anaemia<sup>7</sup>

Graft-versus-host disease

Adenosine deaminase deficiency

## Vascular anomalies

Haemangoendothelioma

Congenital portacaval anomalies

## Idiopathic

Familial

Non-familial (good prognosis)

## Miscellaneous

- Hypoperfusion of liver<sup>7</sup>
- Dubin–Johnson syndrome

## 2. ACUTE HEPATITIS

Acute hepatitis is characterized by liver inflammation and necrosis. The underlying trigger varies, including infective, autoimmune, toxic (e.g. drugs) and metabolic causes.

## 2.1 Acute infective hepatitis

Acute infection of the liver may result from many pathogens. Complete recovery from an infection is dependent on the host’s ability to eliminate the infective agent, resolution of liver inflammation and prevention of infection by effective antibody production.

Symptoms in hepatitis may include:

- Prodrome of malaise
- Anorexia
- Nausea
- Vomiting
- Fever
- Tender hepatomegaly
- Splenomegaly
- Lymphadenopathy
- Rash
- Jaundice

Viruses are the most common cause of acute infective hepatitis.

Causes of acute infective hepatitis	
Viruses	
Hepatotropic viruses	
Hepatitis A	
Hepatitis B	
Hepatitis C	
Hepatitis D	
Hepatitis E	
Non-hepatotropic viruses	
Paramyxovirus (measles)	
Togavirus (rubella)	
Enterovirus	
Echovirus	
Cosackievirus	

## Flavivirus

- Marbug virus

- Ebola virus

Arenavirus (Lassa fever)

Parvovirus B19

Adenovirus

Herpesvirus

- Herpes simplex type 1

- Herpes simplex type 2

- Varicella-zoster virus

- Cytomegalovirus

- Epstein–Barr virus

- Human herpesvirus 6

## Bacterium

*Bartonella henselae/Quintana* spp.

*Brucella melitensis*

*Legionella pneumophila*

*Leptospira icthohaemorrhagica*

*Listeria monocytogenes*

*Mycobacterium tuberculosis*

*Salmonella typhi*

## Protozoa

*Toxoplasma gondii*

## Helminths

Cestodes (tapeworms)

- Echinococcus multilocularis*

- Echinococcus granulosus*

Nematodes (roundworms)

- Ascaris lumbricoides*

- Toxocara canis*

- Toxocara cati*

Trematodes (flukes)

- Schistosoma mansoni*

- Schistosoma japonicum*

- Fasciola hepatica*

## Hepatitis A infection

- The most common form of acute viral hepatitis, accounting for 20–25% of all clinically apparent hepatitis worldwide
- Picornavirus family, RNA virus
- Orofaecal route of spread
- Incubation period 2–6 weeks
- Infectivity from faecal shedding begins during the prodromal phase, peaks at the onset of symptoms and then rapidly declines. Shedding may persist for up to 3 months
- Usually asymptomatic; <5% of infected people have an identifiable illness
- Symptomatic infection increases with age of acquisition
- Mortality rate is 0.2–0.4% of symptomatic cases and is increased in individuals >50 or <5 years
- Morbidity and mortality are associated with:
  - Fulminant hepatic failure
  - Prolonged cholestasis
- Recurrent hepatitis
  - Extrahepatic complications
  - Neurological involvement – Guillain–Barré syndrome, transverse myelitis, postviral encephalitis, mononeuritis multiplex
  - Renal disease – Acute interstitial nephritis, mesangioproliferative glomerulonephritis, nephrotic syndrome, acute renal failure
  - Acute pancreatitis
  - Haematological disorders – autoimmune haemolytic anaemia, red cell aplasia, thrombocytopenic purpura
- Non-specific elevation of conjugated bilirubin and aminotransferase enzymes. Degree of elevation does not correlate with severity of illness or likelihood of complications
- Confirmation of diagnosis relies on detection of:
  - Anti-HAV IgM – indicator of recent infection; peak levels occur during acute illness or early convalescent phase; persists for 4–6 months after infection
  - Anti-HAV IgG – appears early; peaks during convalescent phase; persists lifelong, conferring protection
- Supportive symptomatic treatment and adequate hydration. Complete recovery is usual within 3–6 months
- Active immunization with a formaldehyde-inactivated vaccine is available
- Passive immunization with human normal immunoglobulin offers up to 6 months of protection and is effective if given within 2–3 weeks of exposure

## 2.2 Drug-induced liver disease

Most drugs are lipophilic and are detoxified and excreted in bile. This is achieved by oxidation or demethylation by the cytochrome P450 enzyme system or conjugated by glucuronidation or sulphation by specific transferases. Intermediate metabolites can be potentially harmful and may be detoxified by the binding of glutathione, catalysed by glutathione-S-transferase.

### Mechanism of drug-induced liver disease



- Direct hepatotoxicity – usually dose dependent
- Adverse drug reaction – unpredictable and idiosyncratic

## **Spectrum of drug-induced liver disease**

- Enzyme induction without disease
- Acute hepatitis/hepatocellular necrosis (most common) – paracetamol, methyldopa, isoniazid, halothane, phenytoin
- Cholestasis – erythromycin, co-trimoxazole
- Granulomatous hepatitis – carbamazepine
- Drug-induced chronic hepatitis – methyldopa, nitrofurantion
- Fatty liver – microvesicular (aspirin, valproate, tetracycline) or macrovesicular (amiodarone)
- Fibrosis – methotrexate, vitamin A, actinomycin D
- Vascular disorders – sinusoidal dilatation (oestrogen) or veno-occlusive disease (6-mercaptopurine)
- Hepatic tumours – oral contraceptives

Diagnosis of drug-induced liver disease is usually based on circumstantial evidence and exclusion of other causes.

Withdrawal of the causative drug is the most effective treatment.

Specific therapy is available for paracetamol (*N*-acetylcysteine).

## **3. ACUTE LIVER FAILURE**

Acute liver failure or fulminant hepatitis is rare in childhood. The mortality rate is 70% without appropriate management or liver transplantation. It is the indication for liver transplantation in about 10–20% of paediatric recipients in major transplant centres. The 1-year survival rate is in the range 60–70%.

It is a multisystemic disorder, defined as:

- Severe impairment of liver function (INR >2 and unresponsive to vitamin K)
- $\pm$  encephalopathy (not essential to make diagnosis)
- Associated hepatocellular necrosis
- No previous underlying recognizable liver disease

The most common causes of acute liver failure are:

- In the neonate:
  - Neonatal haemochromatosis
  - Disseminated herpes simplex infection
  - Haemophagocytic lymphohistiocytosis
  - Metabolic causes
- In the older child:

- Viral hepatitis
- Metabolic causes
- Paracetamol toxicity
- Autoimmune hepatitis
- Wilson disease
- Idiopathic

## Causes of acute liver failure

### Infective

#### *Viral*

- Viral hepatitis – A, B, B + D, E
- Non-A–E hepatitis (seronegative hepatitis)
- Adenovirus, Epstein–Barr virus, cytomegalovirus
- Echovirus
- Varicella, measles viruses
- Yellow fever
- Rarely Lassa, Ebola, Marburg viruses, dengue virus, Toga virus

#### *Bacterial*

- Salmonellosis
- Tuberculosis
- Septicaemia

#### *Others*

- Malaria
- *Bartonella* spp.
- Leptospirosis

#### *Drugs*

- Paracetamol
- Halothane
- Idiosyncratic reaction
- Isoniazid
- Non-steroidal anti-inflammatory drugs
- Phenytoin
- Sodium valproate
- Carbamazepine
- Ecstasy

- Troglitazone
- Antibiotics (penicillin, erythromycin, tetracyclines, sulfonamides, quinolones)
- Allopurinol
- Propylthiouracil
- Amiodarone
- Ketoconazole
- Antiretroviral drugs
- Synergistic drug interactions
- Isoniazid + rifampicin
- Trimethoprim + sulfamethoxazole
- Barbiturates + acetaminophen
- Amoxicillin + clavulanic acid

## Toxins

*Amanita phalloides* (mushroom poisoning)

Herbal medicines

Carbon tetrachloride

Yellow phosphorus

Industrial solvents

Chlorobenzenes

## Metabolic

Galactosaemia

Tyrosinaemia

Hereditary fructose intolerance

Neonatal haemochromatosis

Niemann–Pick disease type C

Wilson disease

Mitochondrial cytopathies

Congenital disorders of glycosylation

Acute fatty liver of pregnancy

## Autoimmune

Type 1 autoimmune hepatitis

Type 2 autoimmune hepatitis

Giant cell hepatitis with Coombs test-positive haemolytic anaemia

## Vascular/Ischaemic

Budd–Chiari syndrome

Acute circulatory failure

Heat stroke  
Acute cardiac failure  
Cardiomyopathies

## **Infiltrative**

Leukaemia  
Lymphoma  
Haemophagocytic lymphohistiocytosis

## **Causes of neonatal acute liver failure**

Perinatal herpes simplex virus infection  
Neonatal haemochromatosis  
Galactosaemia  
Tyrosinaemia  
Haemophagocytic lymphohistiocytosis  
Septicaemia  
Mitochondrial cytopathies  
Congenital disorders of glycosylation  
Severe birth asphyxia

## **Biochemistry of acute liver failure**

- ↑ prothrombin time (does not improve with parenteral vitamin K)
- ↑ direct and indirect bilirubin
- ↑ aminotransferase activities (AST), then ↓ as patient deteriorates
- ↑ serum ammonia

## **Complications of acute liver failure**

- Encephalopathy:
  - May be absent or difficult to recognize in children
  - Stage 1 – mild confusion/anxiety, disturbed or reversal of sleep rhythm, shortened attention span, slowing of ability to perform mental tasks (simple addition or subtraction). In young children, irritability, altered sleep pattern, unexplained bursts of excessive crying
  - Stage 2 – drowsiness, confusion, mood swings with personality changes, inappropriate behaviour, intermittent disorientation of time and place, gross deficit in ability to perform mental tasks. In young children, excessive sleepiness, inability to interact with or recognize parents, lack of interest in favourite toys or activities
  - Stage 3 – pronounced confusion, delirious but arousable, persistent disorientation of time and place, hyperreflexia with a positive Babinski sign
  - Stage 4 – comatose with or without decerebrate or decorticate posturing, response to pain present (stage 4a) or no response to pain (stage 4b)

- Renal insufficiency/failure:
  - 10–15% have renal failure, 75% have renal insufficiency as a result of hepatorenal syndrome, direct kidney toxicity or acute tubular necrosis
  - 50% require haemodialysis or haemofiltration support
- Cardiovascular:
  - Early hyperdynamic circulation with decreased peripheral vascular resistance
  - Late haemodynamic circulatory failure as a result of falling cardiac output, depression of brain-stem function or cardiac arrhythmias
- Pulmonary:
  - Aspiration, intrapulmonary shunting, atelectasis, infection, intrapulmonary haemorrhage, respiratory depression or pulmonary oedema
- Metabolic:
  - Hypoglycaemia
  - Acid–base imbalance: respiratory alkalosis, metabolic alkalosis and metabolic acidosis
  - Electrolyte imbalance
- Coagulopathy:
  - Vitamin K deficiency: vitamin K functions as a cofactor for  $\gamma$  carboxylation of glutamic acid, which allows the calcium binding that is required for the activation of factors II, VII, IX, X and proteins C, S and Z of the coagulation cascade
  - ↓ synthesis of clotting factors
  - ↑ fibrinolysis and ↓ clearance of activated factors and fibrin degradation products
  - Thrombocytopenia (correlates with risk of haemorrhage)
- Infections:
  - Poor host defences, poor respiratory effort, multiple invasive lines and tubes
- Others:
  - Adrenal hyporesponsiveness, pancreatitis, aplastic anaemia

Management of acute liver failure involves management of complications, and elucidation and treatment of the cause:

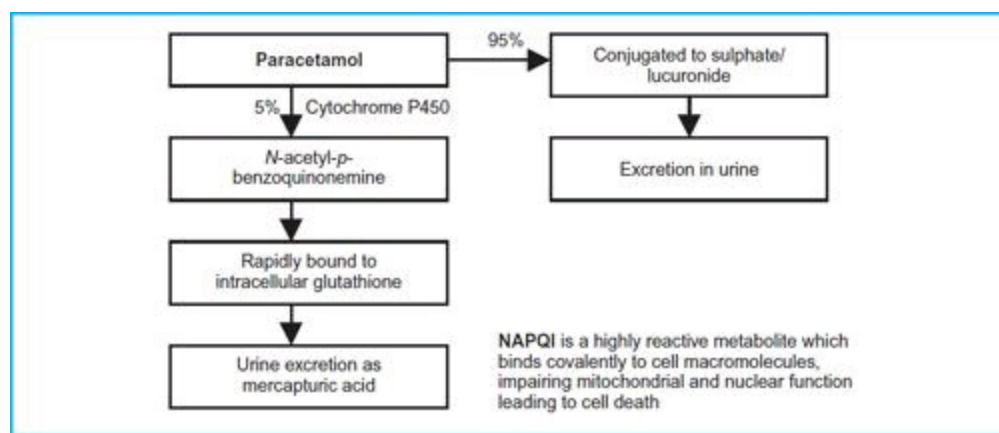
- Discuss/refer to a liver centre
- No sedation unless patient is on assisted ventilation
- Ventilate for respiratory failure, agitation with grade I or II encephalopathy or severe encephalopathy (grade III or IV)
- No coagulation support unless bleeding or for invasive procedures
- Monitoring should involve:
  - Continuous oxygen saturation monitoring
  - At least 6-hourly – neurological observations/vital signs (may need invasive monitoring)/urine output/blood glucose (maintain  $>4$  mmol/l)
  - At least 12-hourly – acid–base/electrolytes/prothrombin time (PT)/partial thromboplastin time (PTT), INR (international normalized ratio)
  - Gastric pH ( $>5$ )
  - Daily or more often – haemoglobin and platelet count
- Fluid balance:
  - 75% maintenance with 0.45% (or less) saline with dextrose

- Maintain circulating volume with colloid, crystalloids or blood products as appropriate
- Haemofiltration if there is renal failure
- Coagulation:
  - Fresh frozen plasma when bleeding
  - Keep platelet count  $>50 \times 10^9/\text{dl}$
- Drugs:
  - $\text{H}_2$ -receptor blockers or proton pump inhibitors (prevent gastrointestinal bleed)
  - Lactulose to achieve two or three stools per day
  - *N*-Acetylcysteine as experimental for non-paracetamol-induced acute liver failure
  - Intravenous broad-spectrum antibiotics and antifungals as prophylaxis
- Nutrition:
  - Enteral feeding (1–2 g protein/kg per day)
  - Parenteral nutrition is rarely indicated
- Specific therapy
  - Paracetamol toxicity – *N*-acetylcysteine (100 mg/kg per day)
  - Hereditary tyrosinaemia – NTBC
  - Neonatal haemochromatosis – iron chelation and antioxidant cocktail/*N*-acetylcysteine (100 mg/kg per day intravenous infusion)/selenium (3 g/kg per day intravenous)/desferrioxamine (30 mg/kg per day intravenous)/prostaglandin E1 (0.4–0.6 g/kg per hour intravenous)/vitamin E (25 U/kg per day intravenous/oral)
  - Mushroom poisoning – benzylpenicillin (1 000 000 U/kg per day) or thiotic acid (300 mg/kg per day)
  - Hepatic support with liver assist devices such as molecular adsorbent recirculating system (MARS) is still under investigation
  - Emergency liver transplantation

### 3.1 Paracetamol (acetaminophen) poisoning

- Mainly one large dose in a suicidal attempt, occasionally accidental over-ingestion over several days
- Direct dose-dependent hepatotoxic effect
- With overdosage, glutathione is depleted and NAPQI (*N*-acetyl-*p*-benzoquinone imine) is not detoxified
- Acute ingestion of 150 mg/kg is likely to cause significant hepatotoxicity
- Triphasic clinical course:
  - Stage 1 (0–24 h) – nausea, vomiting, anorexia
  - Stage 2 (24–48 h) – liver enlarged and tender from hepatic necrosis
  - Stage 3 (48–96 h) – acute liver failure
  - If patient survives stage 3, resolution of liver dysfunction within 4 days to 2 weeks
- Prognosis is bad if:
  - Arterial pH  $<7.3$
  - PTT  $>100$  s or INR  $>6.6$ , creatinine  $>300$   $\mu\text{mol/l}$ , grade III–IV encephalopathy (all three)
- Management:

- Discuss with a liver centre
- *N*-Acetylcysteine infusion 100 mg/kg per day until INR <1.5



Metabolism of paracetamol

### 3.2 Wilson disease

An autosomal recessive disease with incidence of 1 in 50 000; caused by a mutation of the *ATP7B* gene at 13q14.3 (most common *H1069Q*).

Clinical presentation is as follows:

- Asymptomatic: family screening
- Hepatic (5–12 years):
  - Insidious onset with vague symptoms followed by jaundice
  - Abnormal liver function tests
  - Acute hepatic failure
  - Acute hepatitis
  - Chronic liver disease
  - Cirrhosis and portal hypertension
- Neurological (second decade):
  - Deteriorating school/work performance
  - Mood/behaviour changes
  - Incoordination (e.g. deterioration of handwriting)
  - Resting and intention tremors
  - Dysarthria, excessive salivation
  - Dysphagia
  - Mask-like facies
- Others:
  - Sunflower cataracts
  - Acute haemolytic anaemia
  - Renal, cardiac, skeletal abnormalities

Diagnosis is suggested by:

- ↓ total serum copper
- ↓ plasma ceruloplasmin (<200 mg/l)
- ↑ urinary copper (>5  $\mu\text{mol}/24\text{ h}$  [baseline], >25  $\mu\text{mol}/24\text{ h}$  [after penicillamine challenge])
- Liver copper concentration (>250  $\mu\text{g/g}$  dry weight of liver)
- Mutation analysis
- Kayser–Fleischer rings

## **Treatment**

- Penicillamine 20 mg/kg per day (gradually increased from 5 mg/kg per day)
- Pyridoxine 10 mg/week
- Other drugs include: triethylene tetramine dihydrochloride (trientine), zinc sulphate/acetate, tetrathiomolybdate
- Liver transplantation:
  - fulminant hepatic failure
  - chronic, progression of hepatic dysfunction despite treatment

## **4. CHRONIC LIVER DISEASE AND END-STAGE LIVER FAILURE**

Chronic liver diseases of childhood lead to cirrhosis and/or cholestasis. The resulting fibrosis and regenerative nodular formation distort the liver architecture and compress hepatic vascular and biliary structures, resulting in portal hypertension and a vicious cycle of events that worsen the hepatic injury.

## **Diagnostic considerations**

### **Confirming the presence and type of liver disease**

- Compensated – may be asymptomatic
- Decompensated – presence of liver synthetic failure and occurrence of complications
- End-stage – a persistent rise in bilirubin, prolongation of the INR >1.3, persistent fall in serum albumin to <35 g/l, faltering growth despite intensive nutritional support, severe hepatic complications such as chronic hepatic encephalopathy, refractory ascites, intractable pruritus or recurrent variceal bleeding despite appropriate medical management

Determining aetiology

Assessing complications

## **Complications and management**

### **Malnutrition and growth failure**



- Specialized formula ( $\downarrow$   $\text{Na}^+$ ,  $\uparrow$  MCT [medium-chain triglyceride])
- Supplement vitamins A, D, K and E
- $\uparrow$  caloric density of enteral feeds
- Continuous nocturnal nasogastric or nasojejunal feeds
- Parenteral nutritional support

## Portal hypertension

- Major cause of morbidity and mortality (30–50%)
- Portal vein pressure  $>5$  mmHg or portal vein to hepatic vein gradient  $>10$  mmHg:
  - Splenomegaly  $\rightarrow$  hypersplenism
  - Oesophageal, gastric and rectal varices
  - Ascites
  - Encephalopathy
- Prevention and management of oesophageal variceal bleeding:
  - Sclerotherapy
  - Variceal ligation
  - Surgical portosystemic shunts
  - Transjugular intrahepatic portosystemic shunt (TIPS)
  - Oesophageal transection and devascularization
  - Pharmacotherapy, e.g. propranolol
- Factors that predict bleeding
  - Portal vein–hepatic vein gradient  $>12$  mmHg
  - Large, tense varices
  - Red weal marks, red spots on varices
  - Severity of underlying liver disease

## Ascites

- 50% of patients will die within 2 years of developing ascites
- Treatment:
  - Step 1 – sodium restriction (1–2 mmol/kg per day)
  - Step 2 – spironolactone
  - Step 3 –  $\pm$  chlorthiazide/furosemide and fluid restriction
- Spontaneous bacterial peritonitis can occur insidiously and causes high mortality

## Coagulopathy

- Vitamin K malabsorption/deficiency
- Vitamin K-dependent coagulation protein deficiencies (factors II, VII, IX and X)
- Hypofibrinogenaemia and dysfibrinogenaemia
- Thrombocytopenia
- Consumption coagulopathy

- Parenteral vitamin K and transfusion of fresh frozen plasma (prothrombin time >40 s) or platelets ( $<40 \times 10^9/l$ )

## Hepatopulmonary syndrome

- Triad of:
  - Liver dysfunction
  - Intrapulmonary arteriovenous shunts
  - Arterial hypoxaemia – arterial oxygen pressure <9.3 kPa (70 mmHg) in room air and an alveolar/arterial gradient of >20 mmHg (2.7 kPa)
- Type 1 – functional shunt
- Type 2 – anatomical
- Should be suspected if there is increasing history of breathlessness, cyanosis, clubbing and platypnoea
- Platypnoea and orthodeoxia occur because the intrapulmonary arteriovenous shunts occur predominantly in the bases of the lung. Therefore, when sitting up or standing, blood pools at the bases of the lung with resultant increased arteriovenous shunting
- Site and extent of shunt is assessed by:
  - Arterial blood gas analysis
  - Technetium-99m-labelled macroaggregated albumin ( $[^{99m}\text{Tc}]\text{MAA}$ ) study
  - Contrast echocardiogram
- Definitive treatment is with liver transplantation

## Portopulmonary hypertension

- Mean pulmonary artery pressure >25 mmHg, pulmonary capillary wedge pressure <15 mmHg in the absence of any secondary causes of pulmonary hypertension

## Comparison of hepatopulmonary syndrome and portopulmonary hypertension

Hepatopulmonary syndrome	Portopulmonary hypertension
Intrapulmonary vasodilatation	Intrapulmonary vasoconstriction
Alveolar arterial gradient >2.7 kPa (20 mmHg)	Alveolar arterial gradient usually normal
Normal mean pulmonary artery pressure	Mean pulmonary artery pressure >25 mmHg
Perform shunt fraction study	Perform right heart catheterization
Trial of 100% O <sub>2</sub>	Vasodilator therapy trial
Often reversible with liver transplantation	May not reverse with liver transplant
Poor prognosis: PaO <sub>2</sub> <9.3 kPa (300 mmHg) on 100%O <sub>2</sub>	Poor prognosis: pulmonary artery pressure >45 mmHg
Histology: pulmonary artery normal	Histology: pulmonary artery abnormal; concentric medial hypertrophy

## Hepatorenal syndrome

- Diagnostic criteria:
  - Oliguria: urine output  $<1$  ml/kg per day
  - Fractional excretion sodium  $<1\%$
  - Urine:plasma creatinine ratio  $<10$
  - $\downarrow$  glomerular filtration rate,  $\uparrow$  creatinine
  - Absence of hypovolaemia
  - Other kidney pathology excluded
- Type 1 rapidly progressive with poor prognosis
- Type 2 less precipitous loss of renal function
- Mortality rate of  $>90\%$  with severe liver disease
- Reversed with liver transplantation

## Causes of chronic liver disease in children

### Onset in infancy

#### *Structural*

- Extrahepatic biliary atresia
- Alagille syndrome, biliary hypoplasia
- Choledochal cyst, tumours, stones

#### *Storage/metabolic diseases*

- Carbohydrate defects: galactosaemia, fructosaemia, glycogen storage III and IV
- Amino acid defects: tyrosinaemia, urea cycle disorders
- Metal storage defects
- Lipid storage diseases: Gaucher disease, Niemann–Pick type C
- Fatty acid oxidation defects
- Peroxisomal disorders
- Zellweger syndrome
- Mitochondrial disorders
- Progressive familial intrahepatic cholestasis syndrome
- Total parenteral nutrition-associated cholestasis
- Cystic fibrosis liver disease

#### *Haematological*: Langerhans cell histiocytosis

#### *Infection/inflammation*

- Neonatal hepatitis
- Hepatitis B and hepatitis C

### Onset in childhood

All of the above and:

*Autoimmune liver disease*

- Autoimmune hepatitis
- Autoimmune sclerosing cholangitis

*Sclerosing cholangitis*

*Drugs/toxins (e.g. chemotherapy-induced veno-occlusive disease)*

*Fibropolycystic disorders*

*Chronic hepatic venous outflow obstruction:*

- Hepatic vein thrombosis
- Budd–Chiari syndrome
- Veno-occlusive disease
- Cardiac cirrhosis

## 4.1 Autoimmune hepatitis

Autoimmune hepatitis has a 75% female preponderance. Other autoimmune disorders are present in 20% and 40% of first-degree relatives may also have autoimmune disease.

Clinical presentation is variable:

- Acute hepatitis
- Insidious onset
- Portal hypertension

Diagnostic criteria are based on:

- Serum non-organ-specific autoantibodies
- Type 1:
  - Anti-nuclear antibody (ANA)
  - Anti-smooth muscle antibody (SMA)
- Type 2:
  - Anti-liver–kidney microsomal (LKM-1)
  - Up to 20% may not have antibodies detectable at presentation
- Serum biochemistry:
  - ↑ aminotransferases
- Serum IgG:
  - $>1.5 \times$  normal

- Liver histology
- Absence of:
  - Markers of viral infection and metabolic disease
  - Excessive alcohol consumption
  - Use of hepatotoxic drugs

Treatment involves:

- Corticosteroids
- Azathioprine for poor response or as steroid sparing
- Liver transplantation for fulminant hepatic failure or failure of medical therapy

Response to therapy (International Autoimmune Hepatitis Group) is defined as follows:

- Marked improvement of symptoms and return of serum aspartate/alanine aminotransferase (AST/ALT), bilirubin and immunoglobulin levels to completely normal within 1 year and sustained for at least a further 6 months on maintenance therapy,  $\pm$
- Liver biopsy specimen during this period showing minimal activity, or
- Marked improvement of symptoms together with at least 50% improvement of all liver test results during the first month of treatment, with AST/ALT levels continuing to fall to less than twice the upper limit of normal within 6 months during any reduction towards maintenance therapy,  $\pm$
- Liver biopsy within 1 year showing minimal activity

Relapses are common (occurring in 40%).

IgG levels and autoantibody titres correlate with disease activity.

## 4.2 Chronic viral hepatitis

Hepatitis B and C viruses (HBV and HCV) are the top causative agents

### Hepatitis B (a DNA hepadnavirus)

- Worldwide prevalence of 5% (chronic carriers)
- Transmission:
  - Perinatal – hepatitis B ‘e’ antigen (HBeAg)-positive mothers have a 70–90% risk of transmission to their offspring
  - Horizontal – parenteral, sexual and environmental transmission
- Symptomatic acute hepatitis:
  - Complete resolution occurs in 90%
  - Lifelong immunity
- Asymptomatic chronic infection (hepatitis B surface antigen [HBsAg] positive for at least 6 months):
  - 90% progress to chronic liver disease

- Three stages – immune tolerance, immune clearance and residual non-replicative infection
- Chronic infection may lead to cirrhosis and hepatocellular carcinoma

## Serological markers of HBV

Host HBV status	ALT	HBV DNA	Core antibody	Surface antigen	Surface antibody	'e' antigen	'e' antibody
Acute	↑	Detectable	IgM then IgG	+	–	+	–
Chronic							
Immune tolerance	N	High	IgG	+	–	+	–
Immune clearance	↑	Detectable	IgG	+	–	+	–
Non-replicative	N	Undetectable	IgG	+	–	–	+
Resolved	N	Undetectable	IgG	–	+	–	+

\*The 'e' antigen is absent in pre-core mutant.

8

## Immunization

Maternal status			Anti-HBV	HBV vaccine
Surface antigen	'e' antigen	'e' antibody	Immunoglobulin 200 IU within 12 h	Three doses within 12 h, and at 1 and 6 months
+	+	–	Y	Y
+	–	+	N	Y
+	–	–	Y	Y

## Treatment

- Immunomodulation – interferon- $\alpha$ , pegylated interferon
- Antivirals – lamivudine, famciclovir, adefovir
- Not much paediatric experience
- 50% of patients seroconvert with therapy (adult data)
- Liver transplantation for fulminant HBV disease, chronic liver disease, hepatocellular carcinoma

## Hepatitis C infection (an RNA flavivirus)

- Worldwide prevalence is 3%
- Transmission:
  - From blood transfusion or plasma-pooled products
  - Vertical transmission (rare)
- Usually asymptomatic but leads to cirrhosis over years
- One of the most common indications for liver transplantation in adults
- Serology:
  - Anti-HCV antibody positive
  - HCV RNA positive in two consecutive samples
- Treatment:
  - Interferon- $\alpha$  monotherapy
  - Interferon- $\alpha$ /ribavirin combination therapy
  - Paediatric experience is minimal
  - 70% of patients seroconvert with therapy (adult data)

## 4.3 Non-alcoholic fatty liver disease (NAFLD)

- Most common cause of paediatric liver disease; prevalence ranges from at least 3% in children overall to about 50% in obese children
- Occurs more in boys than in girls (2:1), with genetic and racial predisposition
- Associated with obesity although it can occur in non-obese children
- Spectrum of disease from simple steatosis to non-alcoholic steatohepatitis (NASH) to advanced fibrosis and cirrhosis
- Metabolic disease as a result of hyperinsulinaemia and insulin resistance
- Asymptomatic or may present with abdominal pain, hepatomegaly and acanthosis nigricans. An elevated ALT with an enlarged echogenic liver on ultrasonography, in the setting of being overweight or obese and/or evidence of insulin resistance, is highly suggestive, but is not conclusive, for NAFLD
- Liver biopsy is the ultimate standard for the diagnosis and semiquantitative analysis of injury in NASH
- Type 1 NASH (adult pattern) – steatosis with ballooning degeneration and/or perisinusoidal fibrosis in the absence of portal features
- Type 2 NASH – steatosis along with portal inflammation and/or fibrosis in the absence of ballooning degeneration and perisinusoidal fibrosis. Central vein is consistently spared, portal inflammation was predominantly lymphocytic. Type 2 NASH is more common and associated with younger age and obesity
- No proven drug therapy. Management consists of (1) diagnosis and treatment of related metabolic disturbances such as diabetes and hyperlipidaemia, (2) targeting IR by weight loss (healthy lifestyle: diet and exercise) or pharmacotherapy and (3) control of the secondary processes promoting to oxidative stress, inflammation, apoptosis and hepatic fibrosis by using hepatoprotective agents such as antioxidants

## 4.4 Liver transplantation

### Indications for transplantation

- Acute liver failure
- Decompensated chronic liver disease
- Liver-based metabolic diseases
- Liver tumours

### Relative contraindications

- Severe systemic sepsis
- Malignant hepatic tumours with extrahepatic involvement
- Severe, irreversible extrahepatic disease (e.g. structural brain damage, severe cardiopulmonary

disease not correctable with surgery)

- Severe systemic oxalosis with cardiac involvement (haemodynamic instability)
- Mitochondrial cytopathies with multisystem involvement
- Giant cell hepatitis with Coombs test-positive haemolytic syndrome

## **Source of organ**

- Deceased donor
- Living related donor

## **Type of graft**

- Whole liver
- Segmental graft

## **Procedure**

- Orthotopic
- Auxiliary

Lifelong immunosuppression is required with:

- Calcineurin inhibitors:
  - Ciclosporin
  - Tacrolimus
- Renal sparing drugs:
  - Mammalian target of rapamycin (mTOR) inhibitor
  - Sirolimus (mTOR inhibitor)
  - Mycophenolate mofetil
  - Azathiaprine
  - Interleukin-2 receptor antibodies – basiliximab, daclizumab
  - Others – anti-thymocyte globulin, OKT3
- Steroids

## **Postoperative complications**

- Early:
  - Graft failure (primary non-function)
  - Surgical (intra-abdominal haemorrhage, hepatic artery thrombosis, portal vein thrombosis)
  - Drug side effects (renal failure, hyperglycaemia, hypertension)
- After first week:
  - Acute rejection
  - Biliary leaks and strictures
  - Persistent wound drainage



- Sepsis
- Late:
  - Epstein–Barr virus infection
  - Side effects of immunosuppression (renal failure, hyperglycaemia, hyperlipidaemia)
  - Post-transplantation lymphoproliferative disease
  - Graft rejection
  - Late biliary strictures, hepatic artery thrombosis or portal vein thrombosis
  - Recurrent disease (HBV infection, malignant hepatic tumours)
  - New autoimmune hepatitis

## Patient survival

- 1 year – 80–90%
- 5 years – 70–80%
- 10 years – 70–75%

## 5. PORTAL HYPERTENSION

The portal vein contributes to two-thirds of the liver's blood supply. Portal venous pressure is a product of blood flow from the splanchnic circulation and vascular resistance within the liver:

- Portal hypertension is defined as a portal vein pressure  $>5$  mmHg or portal vein to hepatic vein gradient  $>10$  mmHg
- A rise in portal pressure leads to splenomegaly and development of portosystemic collaterals and varices
- A gradient of  $>12$  mmHg is associated with the development of oesophageal varices. The junction between the mucosal and submucosal varices in the lower 2–5 cm of the oesophagus is the usual site of variceal bleeding
- Not all portal hypertension is a result of intrinsic liver disease although chronic liver disease is the most common overall cause. Portal vein occlusion is the most frequent extrahepatic cause of portal hypertension
- Presentation is typically with acute gastrointestinal haemorrhage, splenomegaly or as part of the manifestation of chronic liver disease
- In long-standing disease, varices around the common bile duct may cause portal hypertensive biliopathy resulting in bile duct dilatation and obstructive jaundice
- Rarely, pulmonary hypertension may coexist with portal hypertension, more often in children with chronic liver disease
- Anaemia, leukopenia and thrombocytopenia may result from hypersplenism
- Management:
  - Portal hypertension associated with chronic liver disease:
    - variceal banding or sclerotherapy
    - liver transplantation if variceal bleeding is uncontrolled with therapy
  - Extrahepatic portal hypertension:
    - variceal banding or sclerotherapy

- portacaval or mesoportal shunt
- Pharmacotherapy is not proven in children

## Causes of portal hypertension

### Prehepatic (portal vein occlusion)

#### *General factors*

Developmental malformation

Septicaemia

Thrombophilia

- Myeloproliferative disorders
- Paroxysmal nocturnal haemoglobinuria
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Factor V Lieden mutation
- Anti-phospholipid antibodies
- Factor II gene mutation (*G20210A*)
- Homocysteinaemia

#### *Local factors*

- Umbilical sepsis, catheterization, infusion of irritant solutions
- Intra-abdominal sepsis and portal pyaemia
- Abdominal trauma
- Structural lesions
- Cholangitis/choledochal cyst
- Pancreatitis
- Malignant disease/lymphadenopathy
- Splenectomy

### Intrahepatic

#### *Presinusoidal*

- Hepatoportal sclerosis
- Neoplasia
- Hepatic cyst

#### *Sinusoidal*

- Chronic liver disease and congenital hepatic fibrosis

## ***Postsinusoidal***

- Veno-occlusive disease

## **Posthepatic**

- Budd–Chiari syndrome
- Chronic constrictive pericarditis
- Right ventricular failure

# **6. LIVER FUNCTION TESTS**

This reflects the severity of liver dysfunction but rarely provides diagnostic information on individual diseases.

## **Bilirubin**

- Conjugated (direct) hyperbilirubinaemia:
  - Specific to liver disease
  - Conjugated fraction >20% of total bilirubin is indicative of hepatic dysfunction
- Unconjugated (indirect) hyperbilirubinaemia
- Normal bilirubin levels does not exclude liver cirrhosis

## **Aminotransferases**

- AST and ALT
- Most common tests of liver cell dysfunction
- Intracellular enzymes
- Indicate hepatic necrosis
- AST is produced in the cytosol and mitochondria of the liver, heart, skeletal muscle, kidney, pancreas and red cells
- ALT is found in the cytosol of liver and muscle cells and so is more liver specific
- In isolated AST or ALT elevations, a normal creatine kinase level is helpful in ruling out muscle pathologies
- ALT:AST ratio >1 is suggestive of fibrosis in some liver pathologies such as steatohepatitis and chronic hepatitis C
- There is no correlation between the enzyme levels and the severity of disease
- Levels may be normal in compensated cirrhosis or end-stage liver disease

## **Alkaline phosphatase (ALP)**

- Found in liver, kidney, bone, placenta and intestine

- Reflects biliary epithelial damage
- Children have higher ALP levels than adults (bone isoenzyme)
- Levels are low in zinc deficiency

## **$\gamma$ -Glutamyltransferase**

- Present in biliary epithelia, hepatocytes, renal tubules, pancreas, brain, breast and small intestine
- Reference range is age related. Normal levels in newborns are five to eight times higher than those of adults but reach adult values by 9 months
- Most sensitive test for hepatobiliary disease but cannot differentiate between extra- and intrahepatic biliary disease
- May be normal in familial intrahepatic cholestasis, bile acid synthesis disorders, ARC (arthrogryposis, renal and cholestasis) syndrome and very advanced liver disease

## **Albumin concentration**

- Reflects the synthetic capacity of the liver
- Produced in the liver
- Long half-life (15–20 days), so it is not decreased in acute liver injury
- Levels <35 g/dl in chronic liver disease suggest decompensation

## **Prothrombin time (PT)**

- Prolongation of PT >3 s above normal or INR >1.3 may indicate vitamin K deficiency
- Failure of INR to normalize after a parenteral dose of vitamin K (1 mg/year of age up to a maximum of 5 mg) suggests liver failure
- Reflects the decreased synthesis of factor VII and IX which have short half-lives
- Useful in monitoring progress of acute liver failure

## **Causes of hepatosplenomegaly**

<b>Cirrhosis (early)</b>	biliary atresia, sclerosing cholangitis, congenital hepatic fibrosis
<b>Haematological</b>	thalassaemia, spherocytosis, sickle cell anaemia
<b>Infection</b>	infectious mononucleosis, TORCH, malaria, septicaemia
<b>Immune</b>	juvenile rheumatoid arthritis, systemic lupus erythematosus, immunodeficiency states
<b>Metabolic</b>	$\alpha_1$ -antitrypsin deficiency, tyrosinaemia, cystic fibrosis
<b>Proliferative</b>	leukaemia, lymphoma, Langerhans cell histiocytosis
<b>Storage diseases</b>	Gaucher (long term), Niemann–Pick, mucopolysaccharidoses

## **Causes of hepatomegaly – SHIRT**

## **S – structural**

Extrahepatic biliary atresia, choledochal cyst, intrahepatic biliary hypoplasia, polycystic disease, congenital hepatic fibrosis

### ***Storage/metabolic***

Defective lipid metabolism – Gaucher disease, Niemann–Pick disease, hyperlipoproteinaemias, cholesteryl ester storage disease, carnitine deficiency, mucopolidoses

Defective carbohydrate metabolism – diabetes mellitus, glycosyltransferase deficiency (types 1, 3, 4 and 6), hereditary fructose intolerance, galactosaemia, Cushing syndrome, mucopolysaccharidoses

Defective amino acid/protein metabolism – tyrosinaemia (type 1), urea cycle enzyme disorders

Defective mineral metabolism – Wilson disease, juvenile haemochromatosis

Defective electrolyte transport – cystic fibrosis

Defective nutrition – protein calorie malnutrition, total parenteral nutrition

Deficiency of protease –  $\alpha_1$ -antitrypsin deficiency

Defective bile flow – progressive familial intrahepatic cholestasis syndrome

## **H – haematological**

Thalassaemia, sickle cell disease (chronic haemolysis and transfusion haemosiderosis), acute lymphoblastic, acute myeloid and chronic myelocytic leukaemias

### ***Heart/vascular***

Congestive cardiac failure, constrictive pericarditis, obstructed inferior vena cava, Budd–Chiari syndrome

## **I – infection**

Viral infection – congenital rubella, cytomegalovirus (CMV) infection, Coxsackievirus, echovirus, hepatitis A, B, C, D and E viruses, infectious mononucleosis

Bacterial infections – neonatal septicaemia, *Escherichia coli* urinary tract infection, tuberculosis, syphilis

Parasitic infections – hydatid disease, malaria, schistosomiasis, toxoplasmosis, visceral larva migrans

Fungal infection – coccidioidomycosis

### ***Inflammatory***

Autoimmune liver disease

Inflammatory bowel disease associated liver disease

## **R – reticuloendothelial**

Non-Hodgkin lymphoma, Hodgkin disease, Langerhans cell histiocytosis

## **Rheumatological**

Systemic juvenile chronic arthritis, systemic lupus erythematosus

## **T – tumour/hamartoma**

Primary hepatic neoplasms – hepatoblastomas, hepatocellular carcinoma (hepatoma)

Secondary deposits – neuroblastoma, Wilms tumour, gonadal tumours

Vascular malformation/benign neoplasm – infantile haemangioendothelioma, cavernous haemangioma

## **Trauma**

Hepatic haematoma

# **7. THE PANCREAS**

## **7.1 Acute pancreatitis**

- Defined clinically as the sudden onset of abdominal pain associated with a rise in amylase or lipase of at least three times the upper limit in the blood or urine
- Rare in children
- Involves premature activation of trypsinogen
- Presents with epigastric or back pain. May have prominent nausea and vomiting. Less commonly there may be fever, tachycardia, hypotension, jaundice, and abdominal signs such as guarding, rebound tenderness and a decrease in bowel sounds
- Recurrent acute pancreatitis is seen in 10% of children after a first episode of acute pancreatitis and is commonly associated with structural abnormalities, idiopathic or familial pancreatitis
- The most common cause of familial pancreatitis:
  - Mutations in cationic trypsinogen gene (e.g. *PRSSI*) enhance trypsin activation
  - Mutations in the *SPINK1* (serine protease inhibitor Kazal type 1) gene result in an abnormal pancreatic secretory trypsin inhibitor
  - Mutations of the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene, which reduces the pancreatic fluid secretion capacity, increase the risk of keeping activated trypsin in the pancreas for a longer period of time
- The mainstay of current treatment is analgesia, intravenous fluids, pancreatic rest and monitoring for complications
- Acute pancreatitis scoring system for children that predicts severity of disease and mortality

include the following parameters:

- Age (<7 years)
- Weight (<23 kg)
- Admission white blood cell count ( $>18.5 \times 10^9/l$ )
- Admission lactate dehydrogenase ( $>2000$  IU/l)
- 48-hour trough  $Ca^{2+}$  (<8.3 mg/dl)
- 48-h trough albumin (<2.6 g/dl)
- 48-hour fluid sequestration ( $>75$  ml/kg per 48 h)
- 48-hour rise in urea ( $>5$  mg/dl)
- Each criterion is assigned a value of 1 point, cumulative score predicts the outcome of patients
- 0–2 points – 8.6% severe, 1.4% death
- 2–4 points – 38.5% severe, 5.8% death
- 5–7 points – 80% severe, 10% death
- Surgical management is limited to debridement of infected necrotic pancreas or cholecystectomy or endoscopic sphincterotomy in the presence of gallstones
- A Cochrane review conducted in 2010 suggested that enteral nutrition significantly reduced mortality, multiple organ failure, systemic infections and the need for operative interventions compared with total parenteral nutrition. In addition, there was a trend towards a reduction in length of hospital stay
- Antibiotics are usually not necessary unless in severe pancreatic necrosis
- Octreotide infusions may reduce pancreatic secretions in those with pancreatic fluid sequestration

## Causes of acute pancreatitis

- Idiopathic
- Pancreatitis associated with systemic illness
- Trauma
- Structural abnormalities of pancreas, pancreatic or common bile duct
- Medications (valproate, L-asparaginase, prednisolone, azathioprine, 6-mercaptopurine, furosemide, phenytoin)
- Infections (mainly viral, e.g. mumps, enterovirus, Epstein–Barr virus, hepatitis A, CMV, rubella, Cosackievirus, rubeola, measles, influenza)
- Gallstones
- Familial (*PRSS1*, *SPINK1* or *CFTR* mutation)
- Post-endoscopic retrograde cholangiopancreatography
- Metabolic:
  - Diabetic ketoacidosis
  - Hypercalcaemia
  - Hypertriglyceridaemia
- Cystic fibrosis

## Complications of pancreatitis

---

Local

Systemic

Oedema	Shock
Inflammation	Pulmonary oedema
Fat necrosis	Pleural effusions
Phlegmon	Acute renal failure, coagulopathy
Pancreatic necrosis	Haemoconcentration
Sterile	Bacteraemia, sepsis
Infected	Distant fat necrosis
Abscess	Vascular leak syndrome
Haemorrhage	Multiorgan system failure
Fluid collections	Hypermetabolic state
Pseudocysts	Hypocalcaemia
Duct rupture and strictures	Hyperglycaemia
Extension to nearby organs	

## 7.2 Chronic pancreatitis

- Defined as a complex process beginning with acute pancreatitis and progressing to end-stage fibrosis as the result of recurrent and chronic inflammatory processes
- It is the final common pathological pathway of a variety of pancreatic disorders
- Usually associated with genetic conditions such as cystic fibrosis or hereditary pancreatitis or is idiopathic
- Cystic fibrosis is the most important cause of chronic pancreatitis in children. *CFTR* mutation-associated pancreatitis can be divided into four mechanistic subtypes, where *CFTR*<sub>sev</sub> is the severe *CFTR* mutation phenotype and *CFTR*<sub>m-v</sub> is the mild or variable *CFTR* mutation phenotype:
  - Type 1 – *CFTR*<sub>sev</sub>/*CFTR*<sub>sev</sub> genotype
  - Type 2 – *CFTR*<sub>sev</sub>/*CFTR*<sub>m-v</sub> genotype
  - Type 3 – *CFTR*<sub>sev</sub> or *CFTR*<sub>m-v</sub> plus a second pancreatitis modifier or susceptibility gene (e.g. *CFTR*<sub>sev</sub>/*SPINK1*)
  - Type 4 – *CFTR*<sub>sev</sub> or *CFTR*<sub>m-v</sub> plus a strong environmental risk factor such as alcohol
- Pancreatic insufficiency is a sign of chronic pancreatitis but is not diagnostic. The pancreas has marked functional reserve and has to be severely damaged before functional loss can be clinically recognized
- Faecal elastase <100 µg/g is suggestive of severe exocrine pancreas insufficiency
- Invasive pancreatic stimulation tests are the standard for assessment of pancreatic insufficiency but are not usually indicated
- Chronic pancreatitis with calcifications can be identified on abdominal radiography or by transabdominal ultrasonography. When present, the diagnosis of chronic pancreatitis can be made with 90% confidence
- Other abdominal imaging methods used include computed tomography, endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography, and magnetic resonance imaging or MRCP



(magnetic resonance cholangiopancreatography)

- Genetic testing for *PRSS1*, *SPINK1*, *CFTR* and other mutations can be performed if there is history of recurrent acute pancreatitis, unexplained chronic pancreatitis or presence of a positive family history of hereditary pancreatitis

## 8. FURTHER READING

Al-Omran M, AlBalawi ZH, Tashkandi MF, Al-Ansary LA (2010). *Enteral versus Parenteral Nutrition for Acute Pancreatitis*. The Cochrane Library.

American Association for Study of Liver Disease (2008). Diagnosis and treatment of Wilson disease: An update *Hepatology* **47**:2089–111.

American Academy of Pediatrics (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. American Academy of Pediatrics clinical practice guidelines. *Pediatrics* **114**:297–316.

Dhawan A, Cheeseman P, Mieli-Vergani G (2004). Approaches to acute liver failure in children. *Pediatric Transplantation* **8**:584–8.

Kelly D, ed. (2008). *Diseases of the Liver and Biliary System in Children*, 3rd edn. Oxford: Wiley-Blackwell Publishing.

Kleinman RE, Sanderson IR, Goulet O, Sherman PM, MieliVerhani G (2008). *Walker's Pediatric Gastrointestinal Disease*, 5th edn. PMPHUSA.

National Institute for Health and Clinical Excellence (2012). *CG98 Neonatal Jaundice*. NICE Guideline. London: NICE.

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (2004). Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Paediatr Gastroenterol Nutr* **39**:115–28.

Villatoro E, Mulla M, Larvin M (2010). *Antibiotic therapy for Prophylaxis against Infection of Pancreatic Necrosis in Acute Pancreatitis*. The Cochrane Library, Patient Support Resource: Children's Liver Disease Foundation. Available at: [www.childliverdisease.org](http://www.childliverdisease.org).

---

# Chapter 14

## Immunology

*Pamela Lee and Bobby Gaspar*

---

## CONTENTS

### 1. Key concepts

### 2. The immune system

- 2.1 The lymphoid organs
- 2.2 Cellular origin and components of the immune system
- 2.3 Generation of immune diversity
- 2.4 Induction of self-tolerance
- 2.5 Innate immunity
- 2.6 Adaptive immunity

### 3. Approach to a child with recurrent infections

- 3.1 When to consider a diagnosis of primary immunodeficiency
- 3.2 Categories of primary immunodeficiencies
- 3.3 Common patterns of infections in primary immunodeficiencies
- 3.4 Non-infective manifestations associated with primary immunodeficiencies
- 3.5 Taking a family history for suspected primary immunodeficiency
- 3.6 Examining a child with suspected primary immunodeficiency
- 3.7 Diagnostic approach to common clinical presentations

### 4. Antibody deficiencies

- 4.1 Causes of low immunoglobulins
- 4.2 Defects in early B-cell development
- 4.3 Class-switch recombination defects
- 4.4 Common variable immunodeficiency (CVID)
- 4.5 IgA deficiency
- 4.6 Transient hypogammaglobulinaemia of infancy

## **5. Combined immunodeficiencies**

[5.1 Severe combined immunodeficiency \(SCID\)](#)

[5.2 Combined immunodeficiency](#)

## **6. Other immunodeficiency syndromes**

[6.1 Wiskott–Aldrich syndrome](#)

[6.2 Ataxia telangiectasia](#)

[6.3 DiGeorge syndrome](#)

[6.4 Hyper-IgE syndrome](#)

[6.5 Chronic mucocutaneous candidiasis](#)

## **7. Phagocytic disorders**

[7.1 Congenital neutropenia](#)

[7.2 Schwachman–Diamond syndrome](#)

[7.3 Cyclical neutropenia](#)

[7.4 Leukocyte-adhesion deficiency](#)

[7.5 Chronic granulomatous disease](#)

## **8. Defects of the interleukin-12/interferon- $\gamma$ axis**

## **9. Diseases of immune dysregulation**

[9.1 X-linked lymphoproliferative disease](#)

[9.2 Immunodysregulation, polyendocrinopathy, enteropathy, X-linked \(IPEX\)](#)

[9.3 Chédiak–Higashi syndrome](#)

## **10. Complement deficiencies**

## **11. Hypersensitivity reactions**

## **12. Vaccinating the immunocompromised child**

## **13. Immunosuppressants and immune-modulating agents**

[13.1 T-cell immunosuppressants](#)

[13.2 Clinically used monoclonal antibodies/fusion proteins](#)

[13.3 Interferons](#)

## **14. Haematopoietic stem cell transplantation and gene therapy**

[14.1 Haematopoietic stem cell transplantation](#)

[14.2 Gene therapy](#)

## **15. Further reading**

---

# Immunology

---

## 1. KEY CONCEPTS

### Host–pathogen interaction

- From early life humans come into contact with a wide variety of microorganisms, including bacteria, fungi and virus, which vary in the degree of pathogenicity
- Some microorganisms exist as commensals, some commonly cause infections in the neonatal and childhood period, whereas some remain to be significant human pathogens throughout life
- Immunity against specific infectious agents is brought about by a complicated set of interactions between host and pathogen which, under normal circumstances, maintain an adequate balance between the two
- Increased susceptibility to infectious diseases occurs in individuals with a wide variety of abnormalities including anatomical, metabolic, haematological, oncological and immunological abnormalities

### Functions of the immune system

- Host defence against pathogens
- Recognition of self and non-self
- Sensing of oncogenic stress and elimination of malignant clones

A functional immune system requires:

- Normal development and differentiation of immune cells
- Prompt recognition of a diversity of pathogens and initiation of immune response
- Generation of specific and effective immune response to pathogens
- Immune memory to recall antigens
- Sustenance of immune tolerance to self-antigens
- Immune surveillance to DNA damage
- Check and balance.

Deficient or dysregulated immunity may lead to the following consequences:

- Susceptibility to infections
- Autoimmunity and allergy
- Haemophagocytosis
- Malignancy

## 2. THE IMMUNE SYSTEM

### 2.1 The lymphoid organs

- **Central lymphoid organs:** generation of lymphocytes – bone marrow, thymus
- **Peripheral lymphoid organs:** stations where naïve lymphocytes meet antigens and initiate adaptive immune response – lymph nodes, spleen, mucosal-associated lymphoid tissues in the gut, airway, etc.

### 2.2 Cellular origin and components of the immune system

- Cells of the immune system are derived from bone marrow, pluripotent, haematopoietic stem cells (HSCs), which are capable of cell renewal
- HSCs and the more committed progenitor cells are characterized by the expression of CD34 surface antigen
- **Common lymphoid progenitor** gives rise to T cells, B cells and natural killer (NK) cells
- **Common myeloid progenitor** gives rise to megakaryocyte/erythrocyte progenitor, dendritic cells and granulocyte/macrophage progenitor, which differentiate into neutrophils, monocytes, eosinophils and basophils. Monocytes then differentiate into macrophages in the tissues.

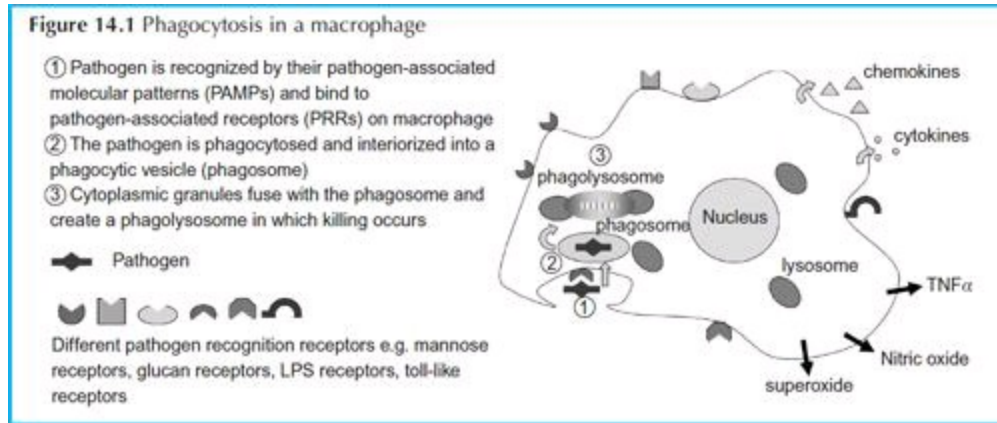
### Phagocytes

- There are three types:
  - Monocytes/macrophages
  - Neutrophils
  - Dendritic cells (DCs)
- Neutrophils and macrophages (Figure 14.1): phagocytosis and intracellular killing of pathogens by various processes including acidification, production of toxic oxygen radicals and nitric oxide, antimicrobial peptides and lysosomal digestion
- Tissue DCs take up pathogens at the site of infection and become activated, after which they migrate to peripheral lymphoid organs, where they present antigens to naïve T cells
- Macrophages and DCs are professional antigen-presenting cells (APCs) that activate T cells and initiate adaptive immune response

### Lymphocytes

- B cells develop in the bone marrow where assembly of pre-B cell and B-cell receptors by V(D)J

(variable, diversity and joining) immunoglobulin (Ig) gene rearrangement occurs. **Immature B cells** migrate to peripheral lymphoid organs, where activation by antigens leads to proliferation and differentiation into antibody-producing **plasma cells** (Figure 14.2)



- T-cell precursors migrate from the bone marrow to the thymus where V(D)J recombination of T-cell receptors (TCRs) occurs, and T-cell precursors develop into **naïve CD4 and CD8 T cells** (Figure 14.3)
- Naïve T-cells that emigrate from the thymus circulate in the bloodstream and enter peripheral lymphoid organs, where activation, clonal expansion and further differentiation into **effector T cells** occur upon antigen encounter (priming)
- Some of the antigen-activated T cells and B cells differentiate into **memory cells**, which promptly differentiate into effector cells upon re-exposure to the specific antigen

## 2.3 Generation of immune diversity

- The variable region of Ig and TCR is encoded by V, D and J gene segments
- The variable region is assembled by random gene rearrangement (**somatic recombination**) initiated by the recombination activating genes (RAGs) in the bone marrow and thymus, where primary Ig and TCR repertoires are generated respectively

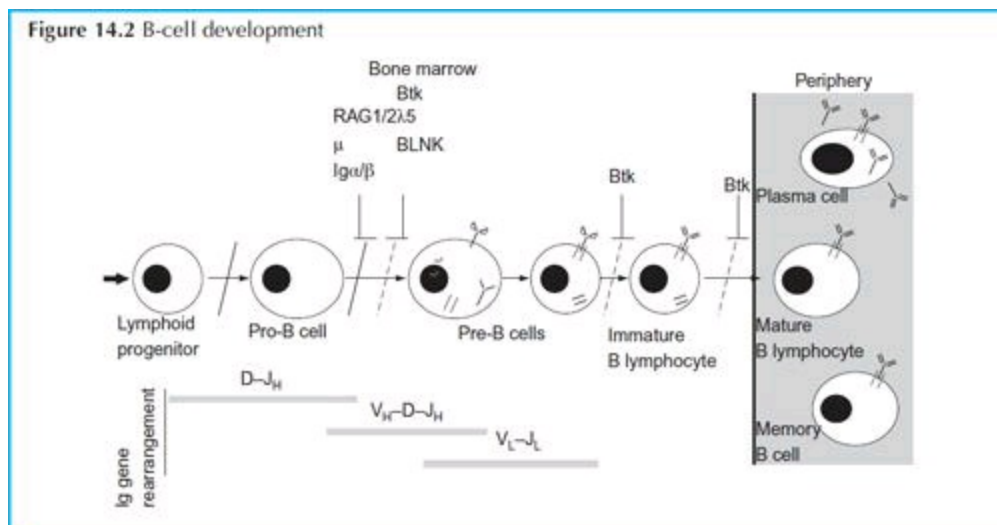
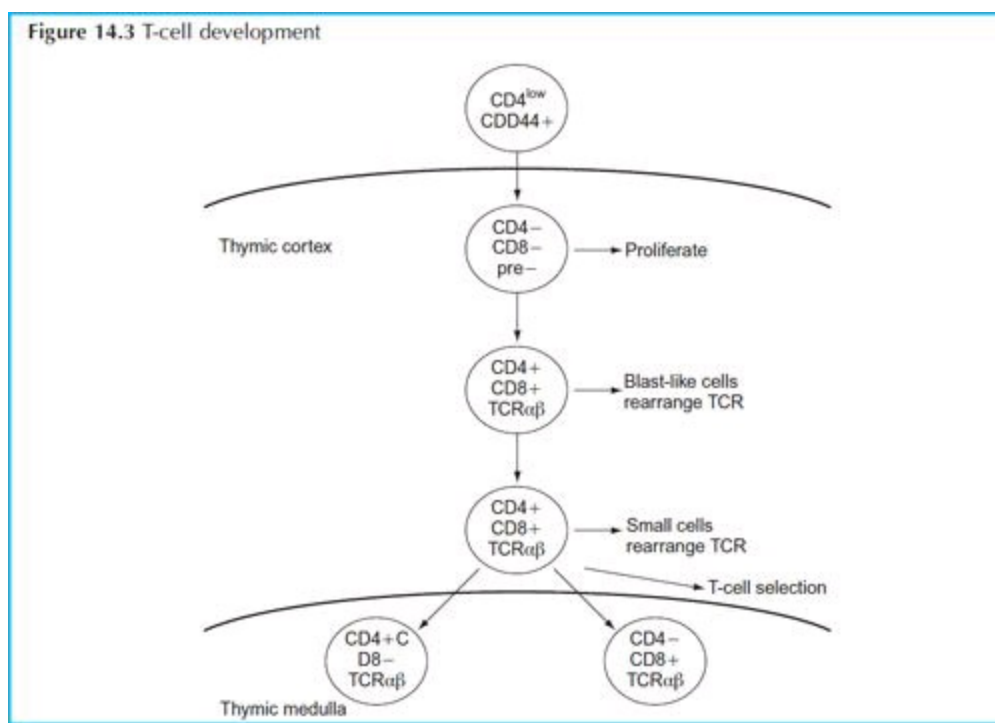


Figure 14.3 T-cell development



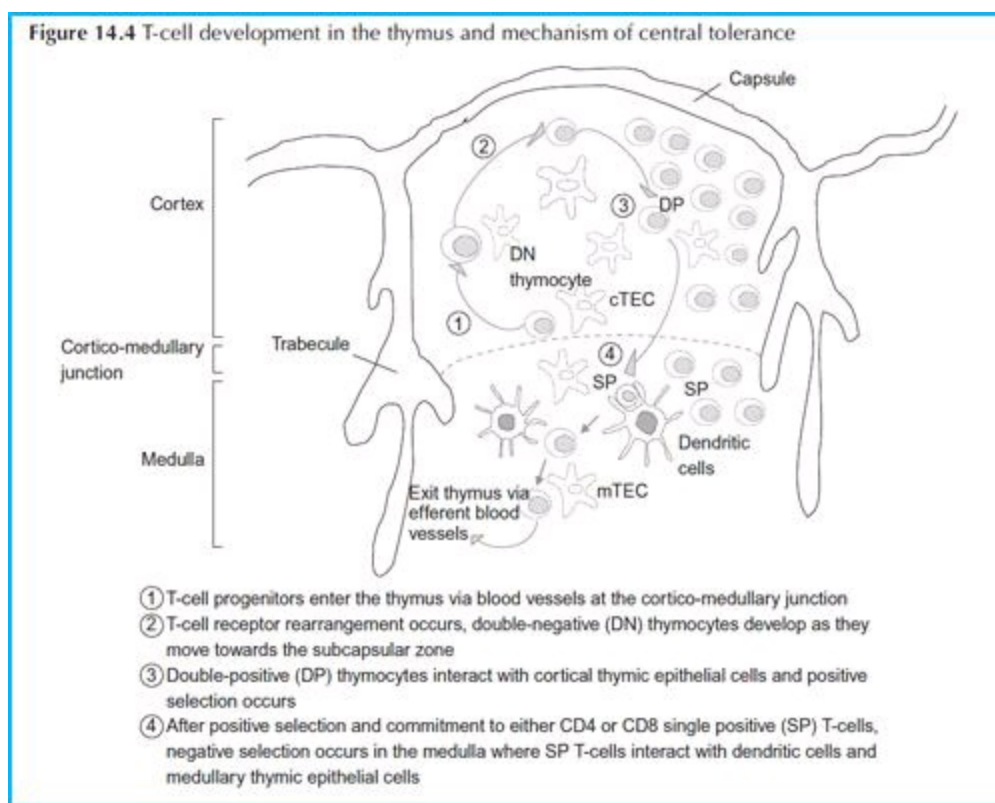
- Further diversity is generated after antigen stimulation of naïve B cells in the germinal centre of peripheral lymphoid organs:
  - **Class-switch recombination:** isotype switching from IgM to IgG/IgA/IgE
  - **Somatic hypermutation:** introducing point mutations to the variable region in antigen-activated B cells to develop high-affinity Ig receptors
- DNA breaks and repair are involved in all the three processes
- Excision of the intervening gene segments during V(D)J recombination of TCR generates **T-cell receptor excision circles (TRECs)**, which is an indicator of intact normal T-cell development and thymic function, and is used as a marker for newborn screening of severe combined immunodeficiency (SCID)

## 2.4 Induction of self-tolerance (Figure 14.4)

- **Central tolerance:** immature B cells and T cells that bind strongly to self cell-surface antigens will be removed from the primary repertoire before they can become bone marrow and thymus, respectively
- Double-positive (CD4<sup>+</sup>CD8<sup>+</sup>) T cells expressing receptors with very low affinity for self-peptide–MHC complexes expressed on cortical thymic epithelial cells die by neglect



Figure 14.4 T-cell development in the thymus and mechanism of central tolerance



- Immature T cells with receptors that bind self-peptide–MHC complex with high affinity will undergo apoptosis (**negative selection** or clonal deletion)
- Only interactions with an intermediate affinity lead to CD4 or CD8 lineage commitment (**positive selection**), followed by passage through the thymic medulla and exit to the periphery
- Lymphocytes newly emigrated from central lymphoid organs will be eliminated if they encounter a strongly cross-linking antigen in the periphery

## 2.5 Innate immunity

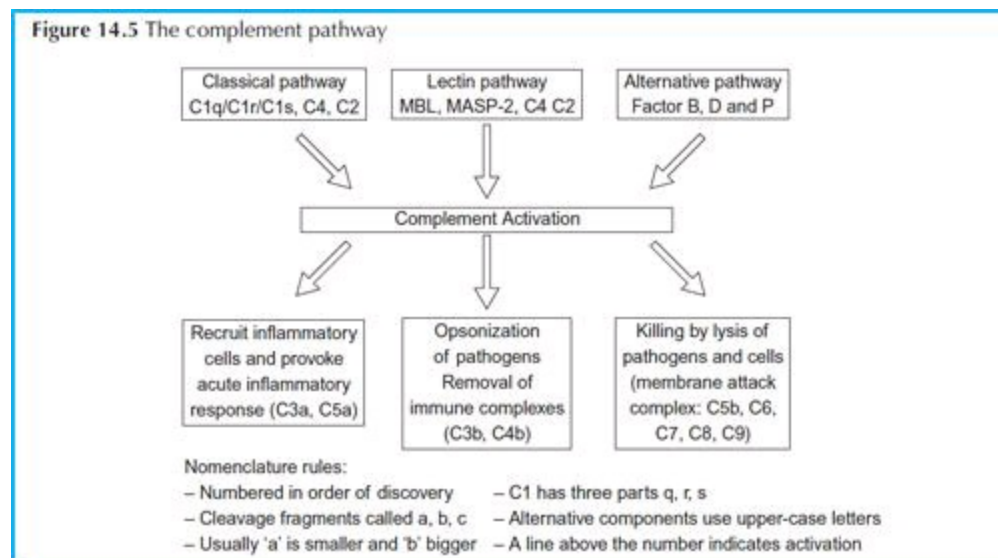
- First line of host defence: barriers that prevent the establishment of infection, e.g. skin, tears, saliva, mucus in the respiratory tract and gut, bile and digestive enzymes in the gastrointestinal tract, acidity of urine and gastric secretions, normal skin and gut commensals that prevent colonization of pathogens
- Once the epithelial defence is breached, innate immune response is activated locally at the site of infection
- Three important functions of innate immunity:
  - **Recognition**: pathogens are recognized by their pathogen-associated molecular patterns (PAMPs) through germline-encoded pattern recognition receptors (PRRs) on macrophages, neutrophils and DCs, e.g. toll-like receptors, mannose receptors
  - **Acute inflammatory response**: pathogens are engulfed and killed intracellularly by activated macrophages and neutrophils, which also secrete cytokines and chemokines and further augment the inflammatory response by recruiting more effector cells and molecules to the site of infection
  - **Induction of adaptive immune response**: activated APCs, e.g. DCs, migrate to lymphoid organs where antigens are presented to T cells and B cells
- **Complement** (Figure 14.5):



- Plasma proteins that are activated by pathogens or pathogen-bound antibody
- Links innate and adaptive immunity
- Classical pathway: C1q, C1r, C1s, C4, C2, C3
- Lectin pathway: mannose-binding lectin (MBL), MBL-associated serine protease (MASP) 1 and 2
- Alternative pathway: factor B, factor D, properdin (upregulating factor)
- Membrane attack complex: C5b, 6, 7, 8, 9
- Down-regulating factors: C1 inhibitor, C4-binding protein, factor H, factor I, S protein
- Membrane control proteins: decay accelerating factor (DAF)

### • Cytokines and chemokines:

- Produced in response to pathogen recognition
- **Cytokines**: soluble factors that mediate signalling between immune cells, may act in an autocrine, paracrine or endocrine manner (see table below)
- Families of cytokines: interleukins, interferons, tumour necrosis factor (TNF) family
- **Chemokines**: chemoattractants recruiting neutrophils, monocytes and other effector cells to the site of infection
- Families of chemokines: CXCL, CCL
- Interferons and cytokines secreted by macrophages activate NK cells which control intracellular infections, especially virus
- Cytokines and chemokines are also secreted by lymphocytes of the adaptive immune system (see [Section 2.6](#))



## Cellular origin and functions of cytokines

Cytokine	Origin	Action
Interleukin-1 (IL-1)	Macrophages	Fever, cachexia, angiogenesis; activates immune cells
IL-2	Th1 (T-helper 1) cells	Proliferation Immune cell activation
IL-4	Th2 cells, mast cells	B-cell class-switching (especially IgE) Proliferation
IL-5	Th2, mast cells	IgA class switching, proliferation
IL-6	T cells, macrophages	T- and B-cell proliferation and differentiation, fever
IL-10	Th2 cells, macrophages	Inhibits Th1 cells and macrophages
IL-12	Th1, B cells, macrophages	Promotes Th1 cytotoxicity and activate NK cells
IL-13	T cells	B-cell growth and differentiation
IL-15	Natural killer (NK) cells	NK-cell growth and survival
IL-17A, IL-17F	Th17, CD8 T cells, NK cells, neutrophils	Proinflammatory action, neutrophil recruitment
TNF- $\alpha$	Macrophages, T cells, B cells, NK cells, Kupffer cells, astrocytes	Inflammation: role in rheumatoid arthritis, Crohn's disease, multiple sclerosis; activates macrophages and other immune cells Cytotoxic for tumours; sometimes promotes tumour growth; angiogenesis
CD40 ligand	T cells, mast cells	Activation of B cells and isotype class switch
Fas ligand	T cells	Cytotoxicity and apoptosis
Interferon- $\gamma$	T cells and NK cells	Macrophage activation, antiviral action

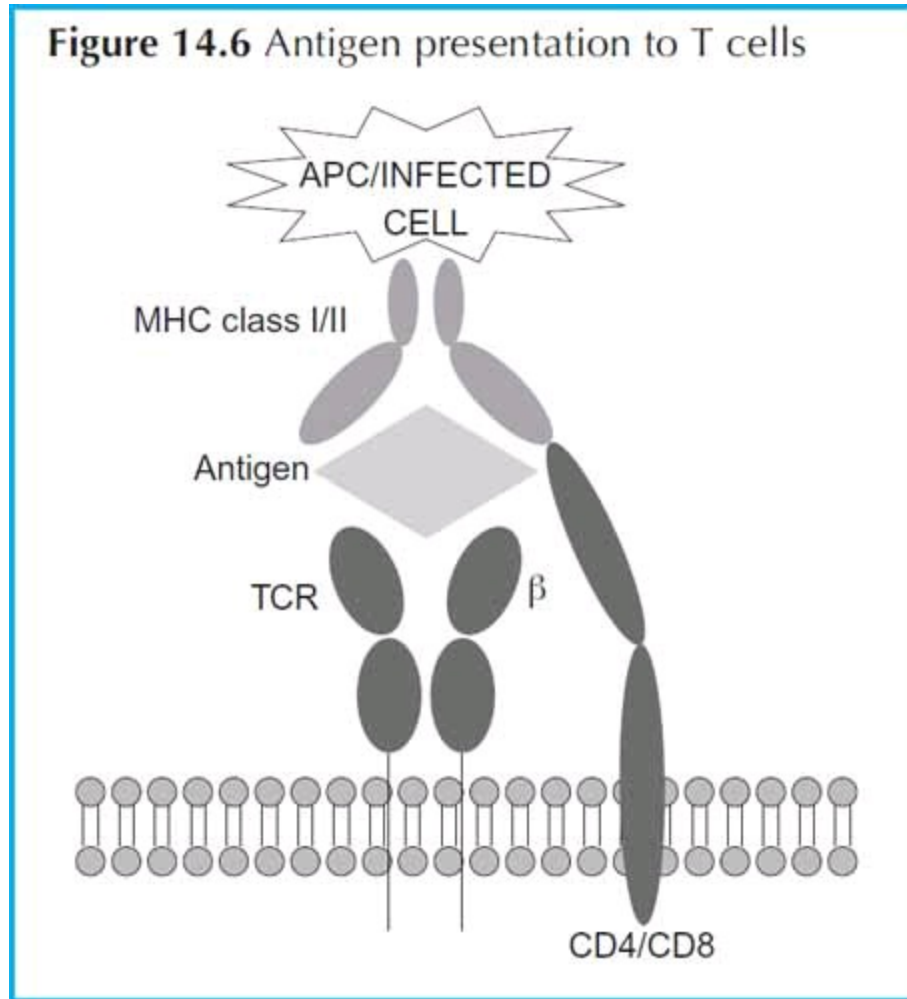
## 2.6 Adaptive immunity

- Divided into humoral and cellular responses
- Humoral immunity: production of specific antibody against an invading pathogen or vaccine antigen
- Cellular immunity: T-cell dependent macrophage activation, cytotoxic T cells

### Effectors of adaptive immunity: antigen recognition and effector functions

- All T-cell effector functions involve cell–cell interactions
- Effector T cells recognize peptide antigens bound to the major histocompatibility (MHC) molecule on the surface of APCs by the T-cell receptor, which delivers the signal for T-cell activation (Figure 14.6)
- **CD8 T cells** (cytotoxic T cells) recognize viral peptides associated with **MHC class I** molecules on the surface of infected cells, and trigger apoptosis by releasing cytotoxic granules into the cytosol of target cell, thus preventing further replication and spread.
  - *Effector molecules*: interferon- $\gamma$ , TNF- $\alpha$ , perforin, granzymes
- **Naïve CD4 T cells** recognize antigens presented by **MHC class II** molecules, and differentiate into distinct functional types of effector cells:
  - **T-helper 1 cells**: activate macrophages to kill the engulfed intracellular pathogens, e.g. mycobacteria, salmonellae
    - *Effector molecules*: interferon- $\gamma$ , TNF- $\alpha$ , granulocyte–macrophage colony-stimulating factor (GM-CSF), CD40 ligand, Fas ligand
  - **T-helper 2 cells** coordinate humoral immune response with T-helper 1 cells by inducing differentiation of naïve B cells into antibody-producing plasma cells

**Figure 14.6** Antigen presentation to T cells

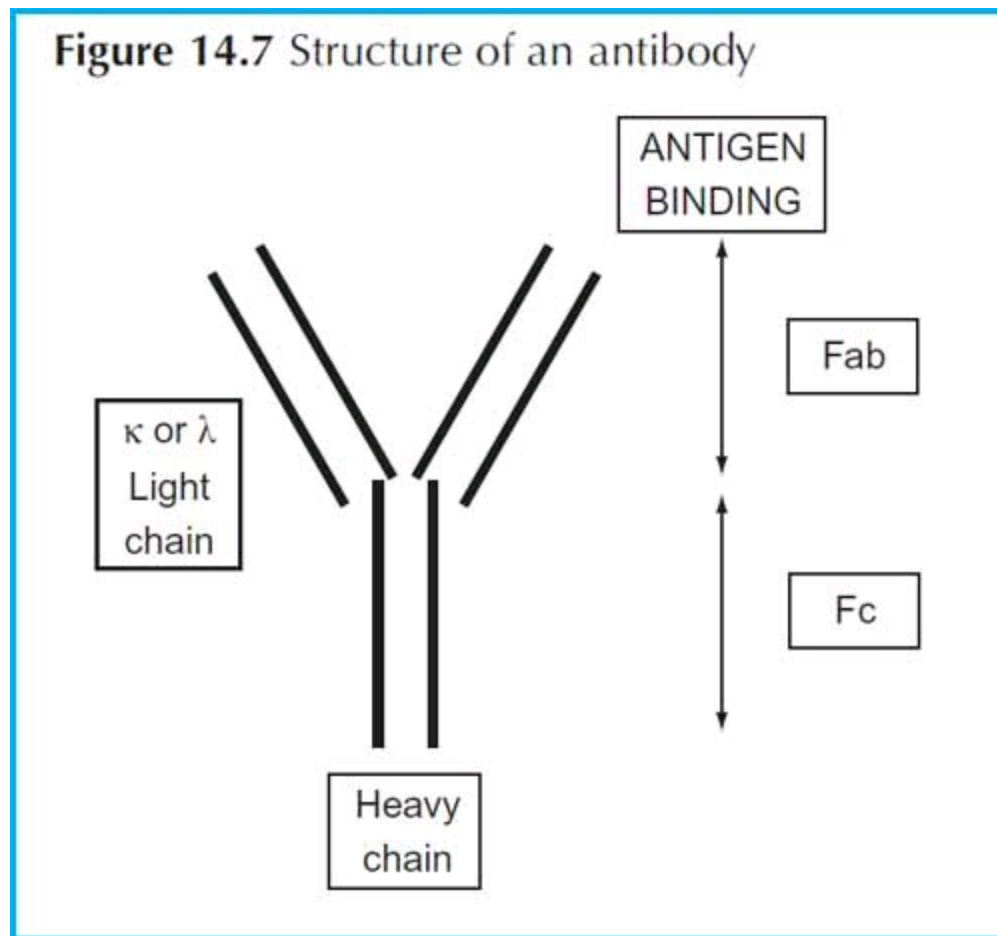


- *Effector molecules*: IL-4, IL-5, IL-13, CD40 ligand
- **T-helper 17 cells**: recruit neutrophils to the sites of infection
  - *Effector molecules*: IL-17A, IL-17F, IL-6
- **T-regulatory cells**: suppress T-cell response and maintain immune homeostasis
  - *Effector molecules*: IL-10, transforming growth factor  $\beta$  (TGF- $\beta$ )
- B-cell receptors recognize extracellular protein antigens of pathogens and differentiate into plasma cells which secrete antibodies, the functions of which include:
  - Binding and neutralization of bacterial toxins and viruses
  - Opsonization of bacteria to facilitate phagocytosis
  - Activation of complement

## Antibody (Figure 14.7)

- The soluble form of B-cell receptor
- Each Ig molecule is composed of two heavy chains and two light chains ( $\kappa$  and  $\lambda$ )
- Each heavy or light chain is composed of constant and variable regions
- The constant region of heavy chain defines the isotype and effector functions (see table below)
- The variable region corresponds to the antigen-binding site
- Digestion with papain releases Fab fragments which bind antigens in the extracellular space
- Fc region has complement-activating domains
- Effector cells recognize antibody-coated pathogens by their Fc receptors which bind to Fc region of

the antibody



### Properties of the five isotypes of immunoglobulin

	IgG	IgM	IgA	IgD	IgE
Size (kDa)	150	950	160	175	190
Cross placenta	Yes	No	No	No	No
Opsonization	+++	+	+	No	No
Complement activation	Classical	Classical	Alternative	No	No
Mast cell sensitization	+	No	No	No	+++

### Generation of immunological memory

- A distinctive feature of specific immunity mediated by humoral and cellular systems
- Immunological memory is sustained by **long-lived antigen-specific lymphocytes** induced by natural infection or immunization
- This provides long-lasting protection upon subsequent challenges with the same pathogen by rapidly mobilizing antigen-specific antibody and effector T cells
- Memory is learnt during the development of the immune system, and explains the difference in frequency of infections between adults and children

## 3. APPROACH TO A CHILD WITH RECURRENT INFECTIONS

### 3.1 When to consider a diagnosis of primary immunodeficiency

- Infections are common in children – school-age children may have 8–10 upper respiratory tract infections per year
- Infections in otherwise healthy children are usually self-limited and uncomplicated, and the child is healthy in between episodes with normal growth and development
- Primary immunodeficiencies (PIDs) are RARE. Extrinsic or secondary causes for recurrent infections should be considered first:
  - Breach of physical barrier:
    - Sinopulmonary: allergic rhinitis, ciliary dysfunction, cystic fibrosis, aspiration pneumonia caused by oromotor dysfunction or gastro-oesophageal reflux
    - Urinary: vesicoureteric reflux
    - Central nervous system: basal skull fracture
    - Skin: atopic eczema, burns
  - Foreign bodies, e.g. indwelling catheters
  - Secondary immunodeficiencies: immunosuppressive therapy, malignancy, malnutrition, protein-losing states (nephrotic syndrome, enteropathy), diabetes mellitus, renal failure
- Primary immunodeficiencies should be considered if a child has:
  - Recurrent/persistent infections of unusual severity, often affecting multiple sites
  - An infection that rapidly progresses and runs a fulminant, life-threatening course
  - Frequent use of antibiotics and suboptimal treatment response
  - Infections caused by opportunistic organisms
  - Failure to thrive
  - Family history of recurrent infections or early infant deaths

### 3.2 Categories of PIDs

PIDs occur as many as 1 in 5000 live births, and are categorized according to the defects of specific immunity:

- Humoral (antibody) deficiencies
- Cellular deficiencies
- Combined deficiencies that affect both humoral and cellular immunity
- Phagocytic defects
- Defects of the innate immunity
- Complement deficiencies
- Autoinflammatory disorders
- Immune dysregulation
- Other well-defined disorders

### 3.3 Common patterns of infections in PIDs

- Recurrent sinopulmonary infections
- Chronic diarrhoea
- Invasive infections, e.g. meningitis, osteomyelitis, deep organ abscess, bacteraemia
- Opportunistic pathogens, e.g. *Pneumocystis jiroveci*, *Cryptosporidium* sp.
- Chronic/extensive candidiasis
- Severe or long-lasting warts, generalized molluscum contagiosum
- Recurrent cutaneous or soft tissue abscess/fistula
- Complications of live vaccines, e.g. BCG, oral polio, rotavirus, varicella

### 3.4 Non-infective manifestations associated with PIDs

- Autoimmunity, e.g. Wiskott–Aldrich syndrome (WAS), hyper-IgM syndrome
- Haemophagocytosis, e.g. familial haemophagocytic lymphohistiocytic (HLH) syndromes
- Lymphoproliferation and malignancy, e.g. autoimmune lymphoproliferative syndrome (ALPS), common variable immunodeficiency (CVID)

### 3.5 Taking a family history for suspected PID

- Family history of recurrent infections, autoimmune and blood diseases, early infant deaths related to infections or unknown cause
- Pattern of inheritance: X-linked, autosomal recessive, autosomal dominant
- Parental consanguinity
- Ethnic origin: ancestral founder mutations in certain ethnic groups
- Examples of X-linked disorders: X-linked agammaglobulinaemia (XLA), X-linked chronic granulomatous disease (X-CGD), X-linked severe combined immunodeficiency (X-SCID, common  $\gamma$ -chain defect), WAS, X-linked lymphoproliferative disease (XLP)
- Examples of autosomal dominant disorders: autosomal dominant hyper-IgE syndrome (ADHIES, caused by *STAT3* deficiency), interferon- $\gamma$  receptor 1 deficiency

### 3.6 Examining a child with suspected PID

The patient should be examined for:

1. Site(s) of infection and its severity
2. Evidence/sequelae of past infections
3. Organ damage, e.g. lung, liver
4. Other non-infective manifestations

A systematic approach to physical examination is shown in the table below.

### Examining a child with suspected primary infection

General	Faltering growth and falling off centile charts, clinical evidence of wasting Finger clubbing indicates chronic lung disease
Skin	Eczema: Wiskott–Aldrich syndrome, hyper-IgE syndrome Petechiae e.g. Wiskott–Aldrich syndrome, autoimmune lymphoproliferative disease Scars e.g. perianal fistula: chronic granulomatous disease Warts e.g. autosomal recessive hyper-IgE syndrome ‘Paper-thin’ scars or poor wound healing: leukocyte adhesion deficiency Complex BCG scar with delayed healing: chronic granulomatous disease Telangiectasia: ataxia telangiectasia Hypopigmentation e.g. Chédiak–Higashi syndrome
Dysmorphic features	Facial dysmorphism e.g. DiGeorge syndrome Some primary immunodeficiency syndromes are associated with skeletal dysplasia
Eyes	Conjunctivitis: antibody deficiency Telangiectasia
Ears	Perforated tympanic membrane, chronic draining of ears: antibody deficiency
Oral cavity	Oral candidiasis: T-cell or phagocytic deficiency, defective innate immunity against fungi Gingivitis/periodontitis: phagocytic deficiency Absent tonsils: severe combined immunodeficiency, X-linked agammaglobulinaemia
Chest	Signs of chronic chest infections/bronchiectasis: antibody deficiency Scars of chest drain insertion for pneumothorax, pleural fluid drainage
Lymph nodes, liver & spleen	Lymphadenopathy and hepatosplenomegaly may be caused by infections, granulomas, lymphoproliferation or malignancy
Joints	Arthritis may be caused by infections or autoimmunity
Neurology	Microcephaly e.g. DNA repair defects Sequelae of previous central nervous system infection Ataxia

### 3.7 Diagnostic approach to common clinical presentations

#### Approach to an infant with recurrent infections and failure to thrive



- Infants are protected by passive transfer of maternal antibodies, which wane after 6 months
- **T-cell and phagocytic deficiencies** should be considered for young infants presenting with recurrent infections and failure to thrive
- Common presentations in a neonate or young infant with primary immunodeficiency:
  - An infant with recurrent bronchiolitic diseases, oral candidiasis, diarrhoea, poor weight gain, skin rash and persistent lymphopenia should raise suspicion for SCID
  - Recurrent infections, bleeding tendency and eczema: Wiskott–Aldrich syndrome
  - Delayed separation of umbilical cord (>3 weeks): leukocyte adhesion defect (LAD)
  - Recurrent perianal abscess, perianal fistula, skin abscess: phagocytic disorder
  - Prolonged discharge from BCG (bacillus Calmette–Guérin) scar, disseminated BCG: chronic granulomatous disease, defects of the IL-12–IFN- $\gamma$  axis, SCID
- Basic investigations:
  - White cell differentials: note that an **absolute lymphocyte count (ALC)  $<2.5 \times 10^9/l$  is abnormal in infants**
  - Lymphocyte subset (enumeration of T, B and NK cells) in infants who are lymphopenic
  - Ig pattern (IgG, IgA, IgM): note that serum IgG in infants under the age of 6 months reflects passive maternal transfer, and local age-specific reference range should be used for interpretation of serum immunoglobulin levels in all ages
  - HIV testing, if clinically appropriate
  - Further evaluations as guided by clinical features and initial investigations (refer to specific disease entities below)
- **SCID is a medical emergency** – infants with suspected SCID should be urgently assessed and managed by paediatric immunologists

## Approach to a child with recurrent sinopulmonary infections

- Sinopulmonary infections include otitis media, sinusitis and bronchopneumonia
- Recurrent chest infections may lead to chronic parenchymal damage and bronchiectasis
- Common causes for recurrent sinopulmonary infections:
  - Atopy: allergic rhinitis, asthma
  - Cystic fibrosis
  - Structural anomalies, e.g. congenital cystic adenomatoid malformation, lung sequestration, primary ciliary dyskinesia
  - Aspiration pneumonia related to swallowing dysfunction or gastro-oesophageal reflux
- Recurrent pneumonia caused by encapsulated bacteria, e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* are common presentations of primary antibody deficiencies
- Patients with cellular immunodeficiencies may present with recurrent bacterial pneumonia, but often have other opportunistic viral or fungal infections
- Basic investigations:
  - Sputum culture
  - White cell differentials: lymphocyte count
  - Ig pattern (IgG, IgA, IgM)



- Total haemolytic complement, C3, C4
- Functional antibodies, e.g. anti-diphtheria, anti-tetanus and anti-pneumococcal antibodies; note that response to polysaccharide antigens is poor until age >2 years
- Lymphocyte subset: T- and B-cell count
- Screening for cystic fibrosis
- CT of the thorax if significant chronic symptoms or abnormalities are apparent on chest X-ray
- Always check that patient has not received blood products or intravenous immunoglobulin (IVIG) before interpreting immunoglobulin levels – if the patient has received such products, it is necessary to wait approximately 3 months before reassessment

## Approach to recurrent skin abscess

- Secondary causes are more common, e.g. atopic eczema and other chronic dermatoses, staphylococcal colonization, diabetes mellitus, inflammatory bowel disease
- PID associated with recurrent skin abscess:
  - Phagocytic disorders, e.g. congenital neutropenia, chronic granulomatous disease, leukocyte adhesion deficiency
  - IL-12–IFN- $\gamma$  axis defects for *Mycobacterium bovis* BCG and atypical mycobacterial infections
  - Hyper-IgE syndrome
  - Wiskott–Aldrich syndrome
- Basic investigations:
  - White cell differentials: neutrophil, lymphocyte and platelet count
  - Blood film: neutrophil and platelet morphology
  - Blood glucose: to rule out diabetes mellitus
  - Skin swab for culture
  - Ig pattern (IgG, IgA, IgM and IgE)
- Specific investigations guided by clinical features and initial investigations (see relevant sections)

## Approach to fungal infections

- Oral or perineal candidiasis is common in neonates and young infants, but unusually severe, treatment-refractory candidiasis warrants attention
- Mucocutaneous candidiasis and invasive fungal infections are common in immunocompromised hosts, e.g. recipients of chemotherapy or immunosuppressants
- Opportunistic fungal infections commonly associated with PID:
  - Yeasts: *Candida* sp., cryptococci
  - Filamentous moulds: *Aspergillus*, *Mucor* spp.
  - Endemic mycoses, e.g. histoplasmosis
- PID associated with fungal infections:
  - Phagocytic disorders
  - Cellular immunodeficiencies, e.g. SCID, DiGeorge syndrome, CD40 ligand deficiency (X-linked hyper-IgM syndrome)
  - Hyper-IgE syndrome
  - Common variable immunodeficiency
  - Chronic mucocutaneous candidiasis syndromes (see [Section 6.5](#))

- Basic investigations:
  - White cell differentials: neutrophils, lymphocytes
  - Blood glucose: to rule out diabetes mellitus
  - Ig pattern (IgG, IgA, IgM and IgE)
  - HIV serology
  - Lymphocyte subset
- Specific investigations guided by clinical features and initial investigations (see relevant sections)

Summary of clinical indications and stepwise approach of immunological investigations for suspected primary immunodeficiencies (see table).

# Clinical indications and stepwise approach of immunological investigations for suspected primary immunodeficiencies

Clinical presentation	Basic investigations	Further investigations
Recurrent sinopulmonary infections	Full blood count Ig pattern Chest radiograph	Neutropenia: to rule out secondary causes (drugs, autoimmunity) Evaluation for antibody deficiency: Panhypogammaglobulinaemia: proceed to lymphocyte subpopulation study, absence of B cells suggests X-linked/AR agammaglobulinaemia Low IgG and IgA but elevated IgM: consider CD40 ligand assay for X-linked hyper-IgM syndrome, and other specialized tests for AR hyper-IgM syndrome Functional antibodies to vaccines and booster response, e.g. tetanus, pneumococci Consider IgG subclass assay Significantly raised serum IgE (often >2000 IU/ml) with compatible clinical features: consider hyper-IgE syndrome Clinical features of ataxia telangiectasia: check serum $\alpha$ -fetoprotein Other investigations: Complement deficiency: haemolytic assay for classic pathway (CH <sub>50</sub> ) and alternative pathway (AP <sub>50</sub> ) Consider mannose-binding lectin (MBL) assay Molecular diagnosis for specific defect Evaluation for severe combined immunodeficiency (SCID) Lymphocyte proliferation test Tests for thymic output: naïve CD4 (CD4+CD45RA+) and CD8 (CD8+CD45RA+), T-cell receptor excision circles (TRECs) Clonality study: V $\beta$ repertoire and spectratype Chimerism study: to rule out maternal engraftment Specialized tests for specific forms of SCID: <ul style="list-style-type: none"> <li>• ADA deficiency: ADA enzyme and dATP levels in blood, urine deoxyadenosine (ADA)</li> <li>• 22q11.2 deletion: fluorescent <i>in situ</i> hybridization (FISH)</li> <li>• Radiosensitivity assay: for diagnosing radiosensitive T<sup>+</sup>B<sup>+</sup>NK<sup>+</sup> SCID</li> </ul> Molecular diagnosis for specific defect Persistent regional/disseminated mycobacterial infection, e.g. BCG and salmonellosis: consider defects in IL12–IFN- $\gamma$ pathway; diagnosis requires cytokine analysis and molecular studies in specialized laboratories
Recurrent infections and failure to thrive in infancy	Full blood count Ig pattern Lymphocyte subpopulation HIV test Chest radiograph	



# Clinical indications and stepwise approach of immunological investigations for suspected primary immunodeficiencies

Clinical presentation	Basic investigations	Further investigations
Recurrent pyogenic infections	Full blood count and blood film review Ig pattern Blood glucose	Further investigations for persistent severe neutropenia: Anti-neutrophil antibodies and other autoimmune markers, e.g. ANA, C3, C4, ANCA Investigation for cyclical neutropenia: full blood count three times a week for 3–6 weeks Bone marrow examination Further investigations for defects in phagocytic function: Chronic granulomatous disease: nitroblue tetrazolium (NBT)/dihydrorhodamine reduction (DHR) test Leukocyte adhesion defect: CD11a/CD18 expression Molecular diagnosis for specific defect Further investigations for X-linked lymphoproliferative disease (XLP) and familial haemophagocytic lymphohistiocytosis (FHLH): Serum soluble CD25 NK cell cytotoxicity XLP: SAP protein assay, genetic study FHLH: granule release assay Molecular diagnosis for specific defect Further investigations for autoimmune lymphoproliferative syndrome (ALPS) CD3+ TCR $\alpha\beta$ + CD4–CD8– double-negative T cells ( $\geq 1.5\%$ of total lymphocytes or $2.5\%$ of CD3+ lymphocytes) in the presence of normal or elevated lymphocyte counts Lymphocyte apoptosis assay Serum IL10, IL18, vitamin B <sub>12</sub> , soluble FAS ligand Molecular diagnosis for specific defect
Fever, lymphadenopathy, hepatosplenomegaly, cytopenia	Blood film review Serum ferritin and fasting triglyceride levels Blood fibrinogen Bone marrow examination	
Cytopenia, chronic lymphadenopathy	Blood film review Lymph node biopsy and detailed histological review Ig pattern	

See text for abbreviations.

## 4. ANTIBODY DEFICIENCIES

### 4.1 Causes of low immunoglobulins

- Primary antibody deficiencies:
  - Account for 65% of all primary immunodeficiencies
  - Three main groups:
    1. Defects in early B-cell development
    2. Class-switch recombination defects
    3. Common variable immunodeficiencies
  - Other less severe forms of antibody deficiencies: selective IgA deficiency, IgG subclass deficiency, transient hypogammaglobulinaemia of infancy (see Sections 4.5 and 4.6)
- **Prematurity**: transfer of maternal antibody to fetus is low before 36 weeks' gestation
- **Excessive losses**: nephrotic syndrome, protein-losing enteropathy, severe burns involving large body surface area
- **Drug-induced**: antimalarials, captopril, carbamazepine, phenytoin, gold salts, sulfasalazine
- **Infections**: HIV, Epstein–Barr virus (EBV), congenital cytomegalovirus, congenital toxoplasmosis
- **Others**: malignancy, systemic lupus erythematosus (SLE)

### 4.2 Defects in early B-cell development

- **X-linked agammaglobulinaemia (XLA)** accounts for 85% of cases; the rest are autosomal recessive forms
- XLA is caused by defect in the Bruton tyrosine kinase (Btk) involved in the B-cell signal transduction pathway, leading to **arrest in B-cell differentiation at the pre-B-cell stage**
- Autosomal recessive agammaglobulinaemia is clinically indiscernible from XLA.
- Defects include components of the pre-B-cell receptor ( $\mu$  heavy chain,  $\lambda 5$  surrogate light chain), signal transduction molecules (Ig $\alpha$  and Ig $\beta$ , BLNK and CD19)
- **Panhypogammaglobulinaemia with low B-cell numbers**
- Pattern of infections:
  - Onset: over 3–6 months of age when maternal antibodies fall below protective level; majority present with recurrent infections before age 2 years
  - Some patients with 'atypical' form may present beyond adolescence and have milder phenotype with small number of circulating B cells and borderline Ig levels
  - Recurrent infections caused by encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, e.g. otitis media, sinusitis, conjunctivitis, pneumonia and empyema, septicaemia, meningitis
  - Giardiasis
  - Pyoderma gangrenosum and pseudomonas sepsis, especially in young infants
  - Enterovirus encephalomyelitis
  - Arthritis caused by *Mycoplasma* and *Ureaplasma* spp.

- Absence of tonsils and lymph nodes is a characteristic physical finding
- Investigations:
  - Low IgG (classically <0.2 g/l), IgA and IgM
  - Poor or absent antibody response to vaccines
  - CD19+ B cells <2% of total lymphocyte count
  - Btk expression in CD14+ monocytes by flow cytometry
  - *BTK* gene mutation analysis
- Treatment:
  - Immunoglobulin replacement
  - Early antibiotic treatment for infections
  - Prophylactic antibiotics if frequent chest infections
- Monitoring:
  - Trough IgG levels to guide the adjustment of immunoglobulin replacement dose
  - Chest X-ray/CT of the thorax to detect development of bronchiectasis

### 4.3 Class-switch recombination defects

- Failure of class switch from IgM to IgA and IgG, resulting in elevated or normal IgM but low IgG, IgA and IgE
- Three groups of disorders:
  1. Defective CD40L–CD40 interaction: CD40 ligand (CD40L) and CD40 deficiencies
  2. Defect in CD40-mediated NF-κB activation: anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) caused by *NEMO* gene mutation
  3. Defects initiating double-stranded DNA breaks in the process of class-switch recombination: activation-induced cytidine deaminase (AID) and uracil-*N*-glycosylase (UNG) deficiencies
- **CD40L deficiency** constitutes 70% of class-switch recombination defects and is transmitted by X-linked inheritance; the remaining are autosomal recessive and very rare

### CD40L deficiency (X-linked hyper-IgM syndrome)

- Class-switch recombination is induced by the binding of **CD40L on activated T cells** and CD40 on B cells
- Defect of CD40L leads to **both cellular and humoral immunodeficiency**
- Most patients present before the age of 2 years
- Pattern of infections:
  - Recurrent sinopulmonary infections caused by encapsulated bacteria
  - *Pneumocystis jiroveci* pneumonia (PCP – formerly *Pneumocystis carinii*)
  - Cryptosporidium enteritis and sclerosing cholangitis
  - Viral infections, e.g. cytomegalovirus, herpes simplex virus, parvovirus B19
  - Mycobacterial infections
  - Patients with associated neutropenia may develop pyogenic or fungal infections
- Other manifestations and long-term complications:
  - Anaemia and neutropenia

- Autoimmunity: thrombocytopenia, seronegative arthritis, inflammatory bowel disease
- Bronchiectasis
- Hepatic complications (sclerosing cholangitis, liver cirrhosis, liver failure, hepatic and biliary tract malignancy) constitute major cause of mortality in adult patients
- Haematological malignancies
- 50% of patients die before the fourth decade despite optimal Ig replacement
- Investigations:
  - Raised/normal IgM, low IgG and IgA
  - T- and B-cell numbers often normal
  - Absent CD40 ligand expression on activated T cells by flow cytometry
  - *CD40L* gene mutation
- Treatment and monitoring:
  - PCP prophylaxis with co-trimoxazole
  - Ig replacement
  - Drinking water must be boiled
  - Screen stool for cryptosporidium infection; however, eradication is often unsuccessful (paramomycin, azithromycin)
  - Monitor liver function and ultrasound, cholangiography and liver biopsy in selected cases
  - Chest imaging to monitor for bronchiectasis
  - Patients with severe neutropenia may require granulocyte colony-stimulating factor (G-CSF)
  - Patients with severe disease despite adequate treatment are considered for haematopoietic stem cell transplant (HSCT)

## 4.4 Common variable immunodeficiency (CVID)

- **Recurrent sinopulmonary infections with reduction in two or more Ig isotypes and impaired vaccine responses usually in patients >2 years**
- The most common form of clinically significant PID; prevalence 1 in 10 000–50 000
- Clinically heterogeneous with wide range of presentations and varying severity
- Typically presents in adolescence and early adulthood, less commonly in late childhood
- Majority of cases are sporadic; 10–25% of patients have familial inheritance, mostly in autosomal dominant fashion
- Single gene defects can be detected in only 10–20% of patients
- Four main groups of clinical manifestations:
  - Infections:
    - Sinopulmonary infections caused by encapsulated bacteria
    - Gastroenteritis: *Giardia intestinalis* (lamblia), *Campylobacter jejuni*
    - Severe varicella-zoster virus (VZV) infection, recurrent herpes zoster
    - Rarely PCP and atypical mycobacterial infections in those with abnormal T-cell function
  - Autoimmunity:
    - Occurs in over half of the patients
    - Haematological: cytopenia, e.g. autoimmune haemolytic anaemia (AIHA), immune thrombocytopenia purpura (ITP)
    - Gastrointestinal: pernicious anaemia, Crohn's disease

- Skin: vitiligo
- Endocrine, e.g. thyroiditis
- Rheumatological: rheumatoid arthritis, SLE, dermatomyositis, Sjögren syndrome
- Granulomatous disease:
  - Non-caseating granulomatous inflammation with sarcoidosis-like lesions involving the lungs, liver, skin, spleen, gastrointestinal tract
- Non-malignant lymphoproliferative disease:
  - Splenomegaly, lymphadenopathy, follicular nodular lymphoid hyperplasia of gastrointestinal tract
- Long-term complications:
  - Bronchiectasis
  - Chronic diarrhoea and malabsorption
  - Gastrointestinal obstruction caused by granuloma
  - Increased risk of malignancy: non-Hodgkin lymphoma, gastric cancers
- Investigations:
  - **Reduction in at least two of IgG, IgA and IgM**
  - **Impaired functional antibody response to vaccines**
  - CD19+ B cells >1% of total lymphocyte count; may have CD4 lymphopenia
  - B-lymphocyte memory panel: reduction in class-switched memory B cells
  - 20% of patients have impaired lymphocyte proliferation
- Management:
  - Ig replacement if significant hypogammaglobulinaemia with poor functional antibody response
  - Prophylactic antibiotics if frequent infections
  - Regular monitoring of blood count, renal and liver function, thyroid function
  - Lung function test and CT of the thorax to monitor development of bronchiectasis
  - Surveillance for autoimmunity and malignancy, e.g. autoimmune markers, endoscopy
  - Immunosuppressive therapy, e.g. steroid for autoimmune diseases and granulomatous manifestations
  - Severe cases may require haematopoietic stem cell transplantation

## 4.5 IgA deficiency

- Estimated prevalence of 1:600–1:300 in white people; the most common form of PID
- Usually asymptomatic
- Increased risk of atopy, and pulmonary and gastrointestinal infections
- Association with IgG2 deficiency
- Possible complications: autoimmunity, ulcerative colitis, Crohn disease, coeliac disease, malignancy
- Diagnosis:
  - Serum IgA <0.07 g/l in a male or female aged >4 years
  - Normal IgG and IgM
  - Normal IgG response to immunizations
  - Other causes of hypogammaglobulinaemia excluded
- 30-40% have antibodies to IgA; there is risk of anaphylactic reactions to blood products or Ig but



the incidence is extremely rare. Individuals who are IgA deficient with anti-IgA should be given an IgA-deficient antibody card

- Management: early use of antibiotics at the onset of infection, prophylactic antibiotics if frequent infections

## 4.6 Transient hypogammaglobulinaemia of infancy (THI)

- Normally serum IgM is detected by 1 week of age and reaches adult levels by 12 months, whereas IgA is detectable by 2 weeks and reaches adult levels by 7 years; IgG reaches adult levels by 7–12 years
- THI refers to delayed maturation of normal Ig production and antibody response
- In THI, there are normal numbers of B cells, distinguishing this from congenital agammaglobulinaemias such as XLA
- Most infants with THI have repeated minor infections; major infections uncommon unless Ig levels are very low and Ig replacement may be necessary during this period
- Serum Ig and vaccine response eventually normalizes with age, and needs to be documented

## 5. COMBINED IMMUNODEFICIENCIES

### 5.1 Severe combined immunodeficiency

- SCID arises from severe defects in both cellular and humoral immunity, typically characterized by **lymphopenia** and **hypogammaglobulinaemia**
- Abnormality in T-cell development and differentiation with variable defects in B-cell and NK-cell development, arising from impairments in:
  - Cytokine signalling, e.g. common gamma chain ( $\gamma_c$ ), IL-7 $\alpha$ , JAK3, STAT5b
  - T-cell receptor signalling, e.g. CD3 subunits, ZAP70
  - Antigen presentation, e.g. MHC class I and II deficiencies
  - V(D)J recombination, e.g. RAG1, RAG2, Artemis, ligase IV
  - Basic cellular processes, e.g. disorder of purine metabolism (adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency) and mitochondrial energy metabolism (reticular dysgenesis)
- Estimated incidence of all forms of SCID is 1:50 000–1:500 000 live births
- Males affected more than females because **X-linked SCID caused by  $\gamma_c$  deficiency is the most common form of SCID**; all the remaining forms are autosomal recessive

### Classical SCID

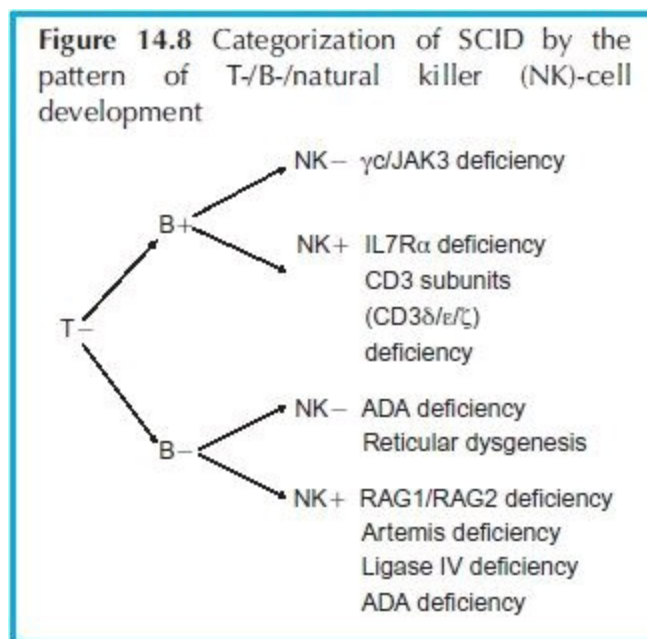
- Infants with classical SCID present early with recurrent, often life-threatening infections at a mean age of 6–7 months
- **Respiratory complications** – interstitial pneumonitis caused by PCP, respiratory syncytial virus, cytomegalovirus (CMV), adenovirus, influenza and parainfluenza infections. Bacterial and fungal

pneumonias are also common.

- **Diarrhoea and faltering growth** – there may be a viral aetiology (rotavirus, adenovirus) but in many cases no cause is defined. Faltering growth as a result of diarrhoea or recurrent infection is seen in nearly all patients.
- **Persistent oral thrush and perineal candidiasis**
- **BCG-related complications**, e.g. abscess formation at the site of inoculation, ipsilateral axillary lymphadenopathy, disseminated BCG
- **Disseminated viral infections**, e.g. CMV hepatitis, encephalitis, viraemia
- **Skin rash** – may be the result of a viral infection but an erythrodermic macular rash is often indicative of maternal T-cell engraftment or Omenn syndrome
- **Absent lymphoid tissues**
- **Investigations:**
  - Lymphopenia: **absolute lymphocyte count  $<2.5 \times 10^9/l$  is abnormal in infants**
  - Chest X-ray: absent thymic shadow, signs of interstitial pneumonitis and hyperinflation
  - Low IgG, IgA and IgM: note IgG level may reflect residual maternal IgG; IgM and IgA production is impaired
  - HIV infection can also present as faltering growth with a similar spectrum of infectious pathogens, and should first be excluded (see Section 7.1, Chapter 15)
  - Red cell adenosine deaminase (ADA) levels and metabolites
  - Lymphocyte subsets: T-, B- and NK-cell numbers and proportions can be indicative of an underlying molecular defect and further investigations, including genetic diagnosis
  - The same immunological phenotype can arise from different molecular defects (genetic heterogeneity – Figure 14.8)

Exceptions to the above scheme (denoted as T+B+ or T+B– SCID) include:

- **Omenn syndrome**: characteristic immunological profile with activated non-functional CD8+ cells and oligoclonality
- **Maternal engraftment**: maternal T cells that are mostly non-functional CD8+ cells



- **Atypical variants:** for many of the defined forms there have been reports of less severe phenotypes where there may be small but abnormal numbers of T/B or NK cells

## Omenn syndrome

- Exaggerated inflammatory response caused by emergence of oligoclonal T-cell populations, often autoreactive in nature
- Clonally expanded T cells infiltrate various tissues:
  - Skin: generalized erythroderma with thickened and leathery skin, alopecia, loss of eyebrows and eyelashes
  - Gut: chronic diarrhoea, protein loss leading to generalized oedema
  - Reticuloendothelial system: lymphadenopathy, hepatosplenomegaly
- Often presents within first few weeks of life
- May have lymphocytosis rather than lymphopenia because of clonal T-cell expansion. **Therefore, a normal ALC does not exclude SCID**
- Eosinophilia and raised IgE is characteristic
- Omenn syndrome is most frequently described in RAG1 or RAG2 deficiency, in which B cells are absent

## Maternofetal engraftment

- Patients with SCID lack functional T cells and cannot reject foreign lymphocytes
- Maternal T lymphocytes that have crossed the placenta engraft in the infant, mediating a graft-versus-host process
- Commonly present as morbilliform erythroderma or papular dermatitis
- A similar condition may occur with viable donor lymphocytes acquired from non-irradiated red blood cell transfusion

## Management

- Specific treatment of infectious complications
- Protective isolation, strict handwashing measures
- Supportive – nutrition, skin care, genetic counselling for family
- Avoid breast-feeding if mother is CMV positive
- CMV negative and irradiated blood products
- Antimicrobial prophylaxis:
  - Co-trimoxazole for prevention of PCP
  - Aciclovir as antiviral prophylaxis
  - Itraconazole/fluconazole as antifungal prophylaxis
- Ig replacement
- Exogenous enzyme replacement using bovine ADA conjugated to polyethylene glycol (PEG-ADA) provides ‘detoxification’ and stabilizes the condition while awaiting haematopoietic stem cell transplantation (HSCT)
- Curative therapies:

- For majority, HSCT is the only curative treatment option; best results if genotypically matched donor, i.e. sibling, is available (>90% success)
- Outcomes for unrelated donor transplantation are approaching those of matched siblings with reduced intensity conditioning and advances in bone marrow transplant (BMT) supportive care
- Gene therapy has been used to treat X-linked SCID and ADA deficiency

## 5.2 Combined immunodeficiency (CID)

- CID refers to a genetically undefined group of immunodeficiencies in which there are variable defects in T- and B-cell function
- CID patients present at a later stage with less severe infections
- Over time, immune function deteriorates leading to recurrent infections and resulting in chronic damage, especially to the liver and lungs
- Principles of management are the same as for SCID
- HSCT is less successful in CID because of underlying chronic organ damage and increased age of transplant

## Purine nucleoside phosphorylase (PNP) deficiency

- Autosomal recessive inheritance
- Lack of expression of PNP and defect in purine salvage pathway
- Triad of immune deficiency, neurological manifestations and autoimmune phenomena
- Infective complications are the most common presenting complaint, but generally at a later age than most SCID types
- Two-thirds have neurological problems, e.g. spasticity, global developmental delay
- One-third develop autoimmune disease including autoimmune haemolytic anaemia and immune thrombocytopenia
- HSCT offers the only cure, but its effect on correcting or preventing further neurological deterioration is controversial

## 6. OTHER IMMUNODEFICIENCY SYNDROMES

### 6.1 Wiskott–Aldrich syndrome

- X-linked inheritance pattern, approximately 1–10 per million live male births
- Classic triad: **thrombocytopenia**, **combined immunodeficiency** and **eczema**; most present before first year of life
- Also susceptible to **autoimmunity**, **lymphoproliferative disease** and **lymphoreticular malignancies** in later life
- Wiskott–Aldrich syndrome protein (WASP) plays a key role in actin cytoskeleton organization in haematopoietic cells
- WASP deficiency leads to global aberrations in innate and adaptive immunity – impaired cellular

migration, phagocytosis, immune synapse formation, NK-cell function, T-cell proliferation, antibody production and memory response, and T-regulatory functions

- Considerable clinical heterogeneity; some patients have thrombocytopenia alone (X-linked thrombocytopenia, XLT) caused by less severe *WAS* mutations
- Bleeding diathesis varies from mucosal bleeding to life-threatening intracranial haemorrhage
- Pattern of infections:
  - Sinopulmonary infections caused by encapsulated bacteria
  - Skin infections
  - Viral infections, e.g. CMV disease
- Autoimmune manifestations include haemolytic anaemia or neutropenia, nephropathy, arthritis, enteropathy, peripheral and large-vessel vasculitis
- Investigations:
  - Diagnosis is suggested by classic clinical phenotype and X-linked pedigree
  - Thrombocytopenia is the most consistent feature
  - Small-sized platelets (may appear as ‘platelet dusts’) on peripheral blood film with low mean platelet volume (MPV, often <5 fl)
  - Ig levels are variable, but antibody responses to polysaccharide antigens are impaired
  - Progressive reduction in T-cell numbers and function
  - Diagnostic confirmation by abnormal WASP expression on immunoblotting or flow cytometry, and *WAS* gene mutation
- Management is oriented to the different clinical problems:
  - Topical treatment for eczema
  - Thrombocytopenia sometimes responds to high-dose Ig (2 g/kg) and steroids
  - Platelet transfusion is indicated in life-threatening bleeding episodes or major surgery
  - Blood product should be irradiated and CMV negative
  - Splenectomy is performed in selected patients to improve platelet count
  - Immune defect is treated by prophylactic antibiotics, Ig replacement and aggressive management of active infections
  - Immunosuppressive drugs may be needed for autoimmune manifestations
  - HSCT is curative and survival is better when performed below the age of 5 years

## 6.2 Ataxia telangiectasia

- DNA-repair defect
- Clinical features:
  - **Immunodeficiency** characterized by lymphopenia and antibody deficiency, with increased susceptibility to recurrent sinopulmonary infections
  - Early onset of progressive **neurological impairment**: cerebellar ataxia and choreoathetosis
  - **Oculocutaneous telangiectasia** in those aged 2 years and above
  - Growth retardation, diabetes and liver dysfunction
  - Increased risk of developing lymphoid malignancies
- Investigations and diagnosis:
  - IgA levels are reduced and serum  $\alpha$ -fetoprotein is raised
  - Cultured cells exhibit increased radiation-induced chromosomal breakage

- Clinical diagnosis is supported by genetic analysis (*ATM* gene mutation)
- Management:
  - Joint management with pulmonologist, neurologist and immunologist
  - The need for antibiotic prophylaxis and Ig replacement depends on the severity of T-cell and B-cell deficiency
  - Lung damage is a major cause of morbidity, regular lung function monitoring and chest imaging are warranted

### 6.3 DiGeorge syndrome

- Developmental defects of the fourth branchial arch, and the third and fourth pharyngeal pouches caused by monosomic deletion of chromosome 22q11.2
- Clinical features:
  - Dysmorphism: lateral displacement of the inner canthi, short philtrum, micrognathia, ear abnormalities
  - Velopharyngeal insufficiency and cleft palate: feeding difficulties, speech problems
- Parathyroid hypoplasia: hypocalcaemic tetany
  - Thymic hypoplasia: majority have partial T-cell defects (reduced T-cell numbers and TCR repertoire diversity), 1% have thymic aplasia and SCID phenotype
  - Cardiac: aortic arch and conotruncal anomalies such as truncus arteriosus, tetralogy of Fallot, interrupted aortic arch or aberrant right subclavian artery
- Susceptibility to infections is multifactorial including underlying cellular and humoral defects, velopharyngeal insufficiency, reflux, cardiac disease and poor nutrition
- Increased incidence of autoimmunity in older children, e.g. immune cytopenia, arthritis, endocrinopathies caused by impaired central tolerance and generation of regulatory T cells
- The most common presentation leading to diagnosis is congenital cardiac malformation, and screening for chromosome 22q11.2 microdeletion is performed as part of the investigations
- Diagnosis is confirmed by the detection of 22q11.2 deletion by fluorescent *in situ* hybridization (FISH); patients with opportunistic infections and lymphopenia should be investigated as for SCID
- Management:
  - Infants with DiGeorge syndrome should undergo immune evaluations and receive irradiated blood products if required for surgical procedures
  - Depending on the severity of immunodeficiency, prophylactic antibiotics and Ig replacement may be indicated
  - Thymus transplantation shows promise in patients with complete DiGeorge anomaly
  - Multidisciplinary inputs from cardiac, respiratory, immunology, general paediatric, speech and language, clinical and education psychology teams

### 6.4 Hyper-IgE syndrome (HIES)

- A triad of (1) high IgE and eosinophilia, (2) eczema and (3) recurrent skin and pulmonary infections
- Autosomal dominant HIES (Job syndrome) is caused by *STAT3* mutation
- Pattern of infections:

- Newborns may present with pustular rash, which evolve into eczematous eruption with chronic *Staphylococcus aureus* colonization
- Cutaneous cold abscesses (lacking sign of inflammation – redness, warmth and pain)
- Otitis media, sinusitis, pyogenic pneumonia caused by staphylococci, pneumococci, and *Haemophilus* and *Pseudomonas* spp.
- Susceptibility to fungal infections due to impaired Th17 function: chronic mucocutaneous candidiasis, pulmonary aspergillosis
- Non-immunological manifestations:
  - Typical facies: prominent forehead and chin, deepset eyes, bulbous nose, coarse facial features, facial asymmetry, high palate
  - Retained primary teeth
  - Scoliosis, fractures with minor trauma, osteoporosis, hyperextensibility
  - Midline anomalies: cleft palate, hemivertebrae
  - Craniosynostosis, Arnold–Chiari I malformation
  - Vascular abnormalities: arterial tortuosity, dilatation, aneurysm
- Food allergy and allergic airway problems are rare
- Complications: pneumatocele and spontaneous pneumothorax, pulmonary haemorrhage, bronchiectasis, increased susceptibility to lymphoma
- Investigations:
  - Eosinophilia, often  $>0.8 \times 10^9/l$
  - Raised serum IgE, usually  $>1000$  IU/ml
  - Reduced Th17 cells
  - *STAT3* gene mutation
- Management:
  - Prophylactic antibiotics and antifungals
  - Antiseptic baths
  - Monitoring of lung function and development of bronchiectasis
- Autosomal recessive HIES:
  - Much rarer than AD-HIES
  - Distinct propensity of developing severe cutaneous viral infections, e.g. molluscum contagiosum, human papillomavirus (warts), herpes simplex virus and VZV
  - Other clinical features: autoimmunity, vasculitis
  - No skeletal or connective tissue abnormalities

## 6.5 Chronic mucocutaneous candidiasis (CMC)

- Presents in childhood with extensive candida infections of the skin, nails and mucous membranes
- Related to defects of dendritic cells or impaired Th1 and Th17 immune response
- Genetic basis of most cases is unknown, but some monogenic syndromes are described
- CMC may be associated with autoimmune endocrinopathies, e.g. hypoparathyroidism and Addison disease in the entity called *autoimmune polyendocrinopathy, candidiasis and ectodermal dysplasia* (APECED) caused by autoimmune regulator (*AIRE*) gene mutation
- Innate immune defects, e.g. CARD9, dectin-1 deficiency
- The mainstay of therapy is prophylactic, systemic antifungal therapy



## 7. PHAGOCYtic DISORDERS

- Neutrophil defects can be classified into:
  - Reduced numbers of circulating neutrophils
  - Defective chemotaxis
  - Defective intracellular killing
- Infections are often caused by *Staphylococcus aureus* and Gram-negative bacteria, e.g. *Pseudomonas* spp.
- Also at risk of fungal infections

### 7.1 Congenital neutropenia

- Failure of differentiation and maturation of the myeloid lineage
- Commonly presents in the first year of life with pyogenic infections often caused by *Staphylococcus aureus*
- Pattern of infections: cellulitis, skin abscess, osteomyelitis, colitis, septicaemia, meningitis
- Diagnosis:
  - Persistent neutropenia  $<0.5 \times 10^9/l$  over a 3-month period
  - Extrinsic causes of neutropenia should be excluded, e.g. viral infection, drugs, alloimmune or autoimmune phenomenon, hypersplenism and malignancy
  - Bone marrow examination: maturation arrest of myelopoiesis at the level of promyelocyte/myelocyte stage
  - Genetic diagnosis for a number of congenital neutropenia syndromes
- Treatment:
  - Aggressive treatment of infections
  - Most patients respond to G-CSF
  - Long-term risk of developing myelodysplastic syndromes and leukaemia
  - HSCT is considered for patients with G-CSF refractoriness, cytogenetic abnormality in bone marrow or frank malignant transformation

### 7.2 Schwachman–Diamond syndrome

- Combination of pancreatic exocrine insufficiency, skeletal abnormalities and recurrent infections of lungs, bones and skin
- Most patients have neutropenia and up to 25% may develop pancytopenia
- The risks of myelodysplasia and leukaemia are increased
- HSCT may be curative

### 7.3 Cyclical neutropenia



- Patients recurrently become neutropenic for 3–6 days over a 21-day cycle (range from 14 days to 36 days)
- Presentation: cyclical pattern of stomatitis, oral ulcers or bacterial infections
- The condition is autosomal dominant and has been linked to elastase (*ELA2*) gene mutation

## 7.4 Leukocyte adhesion deficiency

- Defective binding of circulatory neutrophils to vascular endothelium
- Three forms of LAD with type I being the most common, which is an autosomal recessive defect of  $\delta_2$ -integrin adhesion molecules (CD18) on neutrophils, resulting in defective aggregation and a paradoxical leukocytosis
- Classic presentation:
  - Delayed separation of umbilical cord (beyond 3 weeks)
  - Poor wound healing, often without pus
  - Periodontitis and recurrent orogenital infections
  - Leukocytosis and neutrophilia, may reach up to  $100 \times 10^9/l$  in acute infections
  - Pathogens include *Staphylococcus aureus*, *Aspergillus*, *Candida* spp. and Gram-negative enteric bacteria
- Additional features:
  - LAD type II: dysmorphism, growth and developmental retardation
  - LAD type III: thrombocytopenia
- Investigation:
  - LAD type I: abnormal CD11/CD18 complex expression on neutrophils by flow cytometry, genetic diagnosis (*ITGB2* mutation)
- Management:
  - Prophylactic antibiotics and early treatment of infections
  - HSCT should be considered for severe disease which otherwise results in early death

## 7.5 Chronic granulomatous disease

- A disorder of impaired intracellular killing of pathogens and hyperinflammatory state
- Impaired hydrogen peroxide generation and oxidative burst caused by genetic defects of phox protein subunits constituting the phagocytic NADPH oxidase
- X-linked form of CGD (gp91phox deficiency) accounts for two-thirds of cases and usually presents earlier and with more severe disease than autosomal recessive forms (p47phox, p22phox, p67phox and p40phox deficiencies)
- Pattern of infections:
  - Faltering growth, severe bacterial infections, abscesses (skin, perianal) or osteomyelitis caused by *Staphylococcus aureus* and *Pseudomonas* spp. within the first year of life are common
  - Suppurative adenitis
  - Pneumonia caused by pyogenic bacteria, *Nocardia*, *Aspergillus* spp. and *Burkholderia cepacia*

- Osteomyelitis, e.g. *Staphylococcus aureus*, *Serratia marcescens*
- Non-typhoidal salmonellosis
- BCG-osis and atypical mycobacterial infections
- Hyperinflammatory state: inflammatory bowel disease, granulomatous lesions and lymphadenopathy which may result in intrathoracic, gastrointestinal or urinary obstruction
- Investigations:
  - Nitroblue tetrazolium (NBT)/dihydrorhodamine (DHR) tests
  - Immunoblot or flow cytometric analysis of phox proteins
  - Mutation analysis
- Management:
  - Prophylactic antibiotics and antifungals
  - Steroids to treat granulomatous disease
  - Aggressive use of antifungal agents and granulocyte infusions along with interferon- $\gamma$  may be required to manage severe fungal infections
  - HSCT offers good chance of cure especially in patients with matched sibling donor

## 8. DEFECTS OF THE INTERLEUKIN-12-INTERFERON- $\gamma$ AXIS

- Intracellular pathogens taken up by macrophages or dendritic cells trigger production of **IL-12**, which binds to **IL-12 receptor** on T cells and NK cells to induce **IFN- $\gamma$**  secretion and, in turn, activate phagocytic-mediated killing through release of TNFs
- Defects of the IL-12–IFN- $\gamma$  axis lead to increased susceptibility to intracellular organisms such as *Mycobacterium* and *Salmonella* spp.
- Eight molecular defects have been discovered; the more commonly described forms are defects of IL-12 receptor  $\beta$ 1, IFN- $\gamma$  receptor 1 and IL-12p40
- Infants may present with disseminated BCG and typical mycobacterial infections, and they are usually unable to form granulomas
- Treatment includes antimicrobials and recombinant IFN- $\gamma$
- Successful HSCT has been reported in patients with severe disease

## 9. DISEASES OF IMMUNE DYSREGULATION

### 9.1 X-linked lymphoproliferative disease (XLP)

- Characterized by defective CD8+ and NK-cell cytotoxicity, T-cell cytokine production and activation-induced cell death
- XLP (Duncan disease) is caused by defect of signalling lymphocytic activation molecule (SLAM)-associated protein (SAP) which is critical in the regulation of T-cell stimulation
- Another form of XLP is caused by mutation of the X-linked inhibitor of apoptosis (*XIAP*) gene, with similar clinical features to SAP deficiency
- Unique susceptibility to **EBV-driven lymphoproliferative disease**, and affected boys are well until they contract EBV infection usually at 2–3 years

- Clinical features:
  - Fulminant infectious mononucleosis (60%) manifesting as high fever, generalized lymphadenopathy, splenomegaly and cytopenia, often complicated by secondary haemophagocytic lymphohistiocytosis (HLH) characterized by T- and B-cell lymphoproliferation
  - Lymphoma (30%)
  - Dysgammaglobulinaemia (30%)
  - Aplastic anaemia (3%)
  - Phenotypes can exist together or evolve from one to another
  - EBV is not always the trigger for these dysregulatory phenomena, and a significant number of boys are EBV negative
- Investigations and diagnosis:
  - Features of HLH: pancytopenia, ↑ serum ferritin and triglyceride, ↓ fibrinogen, haemophagocytosis in bone marrow, spleen, lymph node or cerebrospinal fluid, ↑ soluble CD25 in blood
  - Hypogammaglobulinaemia, some with dysregulated raised IgM production
  - Lymphocyte subset: reduced or absent NK T cells, reversed CD4:CD8 ratio
  - Impaired NK-cell cytotoxicity
  - Reduced or absent SAP expression by flow cytometry
  - Mutation of *SH2D1A* which encodes SAP
- Management:
  - Treatment of HLH with immunosuppression and chemotherapy (etoposide, dexamethasone, ciclosporin)
  - Anti-CD20 monoclonal antibody (rituximab) is used to treat EBV infection by eliminating B cells
  - Ig replacement
  - HSCT offers the only curative option but risk is high if remission of HLH is not achieved by medical treatment
  - Fulminant infectious mononucleosis carries a high mortality rate >90%, and the major cause of death is hepatic necrosis
  - In affected boys identified by family history, prophylactic antibiotics and Ig replacement do not provide protection from severe EBV infection

## 9.2 Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)

- Onset: infancy
- An immunodysregulatory syndrome with a clinical triad of:
  - **Enteritis:** commonly presents with intractable diarrhoea, failure to thrive; bowel histology shows villous atrophy with lymphocytic infiltrate
  - **Endocrinopathy:** type 1 diabetes mellitus, hypothyroidism
  - **Dermatitis:** eczematous skin rash
- Susceptibility to bacterial, viral and fungal infections secondary to enteropathy, dermatitis and immunosuppression
- Other autoimmune manifestations: cytopenia, glomerulonephritis, hepatitis

- Investigations:
  - Eosinophilia is common
  - May have hypoalbuminaemia caused by protein-losing enteropathy
  - Hypergammaglobulinaemia
  - Autoantibodies, e.g. anti-islet cell antibodies
  - Lack of FOXP3 expression in CD4+CD25+T cells; mutation in *FOXP3* gene
- Management: immunosuppression, HSCT
- High rate of mortality; most die before the age 2 years without HSCT

### 9.3 Chédiak–Higashi syndrome

- A lysosome-related organelle disorder with defective exocytosis of intracellular proteins
- Affected cell types: NK cells, cytotoxic T cells, phagocytes, melanocytes, neural cells
- Clinical features:
  - **Immunodeficiency:** recurrent pyogenic infections of the chest and skin
  - **Neurological:** weakness, ataxia, peripheral neuropathy, progressive neurodegeneration
  - **Hypopigmentation:** oculocutaneous albinism
  - **Accelerated phase:** haemophagocytosis, lymphocyte and monocyte infiltration of tissues, often fatal
- Investigations and diagnosis:
  - Peripheral blood film: giant intracytoplasmic lysosomal granules in neutrophils
  - Light microscopy of hair shaft: aggregates of pigment granules
  - Abnormal granule release assay
  - Mutation of the lysosomal trafficking regulator (*LYST*) gene
- Management: HSCT is the definitive treatment, and should be undertaken before the onset of the accelerated phase if a matched donor is available

## 10. COMPLEMENT DEFICIENCIES

- Susceptibility to pyogenic infections caused by encapsulated bacteria, usually less severe in deficiency of the early complement pathway components (C1, C4, C2) compared with deficiency of properdin, C3 or terminal component
- Deficiencies of early complement pathway components more commonly present with autoimmunity, e.g. systemic lupus erythematosus, glomerulonephritis
- Reduction in serum C3, C4 or both; more likely to be a consumptive process, e.g. autoimmune disease, or infections than congenital complement deficiencies
- Functional screening assays of the classic or alternative pathways can be performed in patients with suspected complement deficiencies

### Inherited complement deficiencies and clinical manifestations

Defect	Pathway	Clinical manifestations
C1q, C1r, C1s, C4, C2 C3	CP Common to CP, AP and LP	Encapsulated bacterial infections, autoimmunity (mainly SLE) Severe pyogenic infections, glomerulonephritis
C5, C6, C7, C8, C9	Membrane attack complex	Recurrent <i>Neisseria</i> infections, SLE, less common with C9
Mannose binding lectin	LP	Predisposition to pyogenic infections in early childhood, mostly asymptomatic
Factor D	AP	Recurrent <i>Neisseria</i> infections
Properdin	AP stabilizer	Recurrent <i>Neisseria</i> infections
Factor H, Factor I	AP inhibitor	Recurrent pyogenic infections related to C3 deficiency; also associated with glomerulonephritis and HUS
Decay accelerating factor	AP and MAC inhibitors	Paroxysmal nocturnal haemoglobinuria: haemolysis, thrombosis
C1 inhibitor	CP inhibitor	Hereditary angioedema

AP, alternative pathway; CP, classic pathway; HUS, haemolytic–uraemic syndrome. LP, lectin pathway, MAC, membrane attack complex; SLE, systemic lupus erythematosus

## Hereditary angio-oedema

- Deficiency of C1 inhibitor leads to spontaneous activation of the classic complement pathway and the kinin-releasing system
- Recurrent acute attacks of facial, airway and periorbital oedema, limb swelling and abdominal pain
- The swelling builds up over 1–2 hours and spontaneously subsides within 48–72 hours; does not respond to antihistamines, adrenaline or steroid
- Laryngeal oedema can cause fatal upper airway obstruction
- Attacks may be triggered by trauma, including surgery and dental procedures, cold exposure, anxiety and emotional stress
- Often manifests in older children or teenagers and tends to persist throughout lifetime
- **Autosomal dominant inheritance**; positive family history is common
- Diagnosis: characteristic clinical features, low C4, reduced C1 inhibitor level
- Management: airway and fluid management, C1 inhibitor concentrate (or fresh frozen plasma if not available); prophylactic drugs, e.g. danazol, if attacks frequent or severe

## 11. HYPERSENSITIVITY REACTIONS

Type 1	Type 2	Type 3	Type 4	Type 5
Immune mediator Antigen	IgE Soluble	IgG, IgM Cell surface	IgG Soluble	T cells Soluble or cellular
Mechanism	Mast-cell degranulation	Altered signalling complement activation	Immune complexes	Th1 (IL-2, IFN- $\gamma$ ) Th2 (IL-4, IL-5) Cytotoxic T cells
Clinical conditions	Asthma Food allergy Disease of hayfever Anaphylaxis	Haemolytic Arthus reaction Newborn penicillin allergy	Serum sickness dermatitis Erythema nodosum	Contact conditions Tuberculin Chronic asthma

## 12. VACCINATING THE IMMUNOCOMPROMISED CHILD

- Live vaccines are contraindicated in patients with severe T-cell deficiency, e.g. SCID, Wiskott–Aldrich syndrome, CD40 ligand deficiency and other major immunodeficiencies, e.g. LAD, HIES

- BCG should not be given to patients with CGD and IL-12–IFN- $\gamma$  axis defects
- Live vaccines should not be given to patients receiving chemotherapy and systemic immunosuppressive therapy
- Vaccines are not likely to be beneficial while the patient is on Ig replacement, and should be deferred until at least 3 months after stopping Ig
- Patients with antibody deficiency will benefit from seasonal influenza immunization
- Patients with sickle cell disease, nephritic syndrome, malnutrition and chronic disease should receive pneumococcal (if not already given according to standard immunization schedule) and seasonal influenza immunizations
- Post-splenectomy patients should receive pneumococcal, *Haemophilus influenzae* type b (Hib) and meningococcal C conjugate vaccines, if not already given according to standard immunization schedule
- Consider giving varicella-zoster vaccine to seronegative family members to provide indirect protection

## 13. IMMUNOSUPPRESSANTS AND IMMUNE-MODULATING AGENTS

### 13.1 T-cell immunosuppressants

Drug	Indications	Major side effects
Prednisolone	Prevent graft rejection and graft-versus-host disease (GvHD) Immunosuppression for other indications	Hypertension, thin skin, truncal obesity, proximal myopathy
Ciclosporin	Prevent graft rejection and GVHD Suppress autoimmune disease	Nephrotoxicity, hirsutism, hypertension
Tacrolimus	Prevent rejection	Nephrotoxicity, neurotoxicity, cardiomyopathy
Mycophenolate mofetil (MMF)	Prevent rejection	Leukopenia, marrow suppression
Azathioprine	Prevent graft rejection, treatment of autoimmune diseases	Marrow suppression, hepatotoxicity

### 13.2 Clinically used monoclonal antibodies/fusion proteins

Drug	Target	Indication
Rituximab	CD20 on B cells	B-cell lymphoma, lymphoproliferative disease
Daclizumab	Anti-CD25	Inflammation caused by activated T cells
Infliximab	Tumour necrosis factor (TNF)- $\alpha$	Rheumatoid arthritis, juvenile idiopathic arthritis, Crohn disease
Etanercept	TNF- $\alpha$ receptor	Juvenile idiopathic arthritis, rheumatoid arthritis
Anti-thymocyte globulin (ATG)	T cells	T-cell depletion
OKT3	T cells	T-cell depletion
Campath	CD52 on human T and B cells	T-cell depletion in bone marrow transplantation and treatment of certain types of lymphomas

### 13.3 Interferons (IFNs)



Drug	Possible indications	Side effects/Comments
IFN- $\alpha$	Myeloma, renal carcinoma, melanoma	Flu-like illness, fever, myelosuppression, depression
IFN-2 $\alpha$	Hepatitis C	Given with ribavirin
IFN- $\beta$	Multiple sclerosis	Fever, flu-like illness
IFN- $\gamma$	Mycobacterial infection, chronic granulomatous disease	Fever, flu-like illness

## 14. HAEMATOPOIETIC STEM-CELL TRANSPLANTATION AND GENE THERAPY

### 14.1 Haematopoietic stem cell transplantation

- Offers a curative option for haematological malignancies, congenital immunodeficiencies, haemoglobinopathies, inherited metabolic defects and autoimmune conditions
- Source of haematopoietic stem cells (HSCs):
  - Bone marrow: in addition to HSCs, also contains mesenchymal stem cells
  - Peripheral blood stem cells harvested by leukapheresis after giving the donor a course of G-CSF for stem cell mobilization, a high stem cell dose can be obtained but risk of graft-versus-host disease (GVHD) is higher
  - Umbilical cord blood: advantage of less GVHD and faster immune reconstitution, but the number of cells that are available in a cord blood unit may limit its use in older children and adults
- Donor source:
  - **Autologous**: collected from the patient, usually before intensive chemotherapy or radiotherapy for solid tumours, and reinfused to rescue the haematopoietic system; also used for some autoimmune conditions, e.g. SLE, juvenile idiopathic arthritis
  - **Allogeneic**: matched sibling donor (offers best outcome among all donor sources), matched family donor (often in consanguineous families), haploidentical parent, matched unrelated donor, unrelated cord blood units
  - Indications: relapsed leukaemias, primary immune deficiencies, haematological disorders (Fanconi syndrome, thalassaemia, sickle cell disease) or metabolic conditions (adrenoleukodystrophy, Hurler syndrome, osteopetrosis)
- Conditioning:
  - Chemotherapy and/or radiotherapy is used to eradicate disease (e.g. leukaemia), prevent rejection of donor stem cells by existing host immune system and facilitate engraftment of donor cells in the host bone marrow; in some cases, e.g. X-linked SCID, conditioning may not be necessary depending on the level of residual immunity
- Early post-transplantation complications:
  - Infections: bacterial, fungal and viral e.g. EBV, adenovirus, CMV
  - GVHD: mediated by T cells in the graft and graded I–IV on the basis of skin rash, liver impairment and gastrointestinal involvement. Note that donor T cells can mount a graft-versus-leukaemia effect which helps to eradicate malignant cells in recipients with leukaemia
  - Engraftment syndrome
  - Graft rejection or failure
  - Organ complications related to toxicities of conditioning agents: mucositis, haemorrhagic cystitis (cyclophosphamide), veno-occlusive disease (alkylating agents), thrombotic microangiopathy

- Late post-transplantation complications: chronic GVHD (skin, gut, liver, sicca syndrome, bronchiolitis obliterans, cytopenia), incomplete immune reconstitution, growth retardation and endocrine problems, cognitive impairment in some patients

## 14.2 Gene therapy

- Gene therapy has been used to treat X-linked SCID, ADA deficiency, Wiskott–Aldrich syndrome and chronic granulomatous disease
- The patient's own bone marrow stem is harvested for collection of stem cells, followed by ex vivo gene transfer of the therapeutic gene into the patient's stem cells, using a non-replicating viral vector
- The modified viral vector stably integrates into the genome of the recipient's stem cells
- The gene-modified stem cells are then infused back into the patient
- Immune reconstitution follows over a period of several months
- Although this approach has been shown to be potentially curative, there is a risk of insertional mutagenesis whereby oncogenes are activated by the integrating viral vector, leading to the development of leukaemia, which occurred in several gene therapy recipients
- Continuous efforts are made in improving vector design, gene transfer efficiency and safety, and currently gene therapy is offered to patients with no HLA-matched donors available for transplantation

## 15. FURTHER READING

Arason GJ, Jorgensen GH, Ludviksson BR (2010). Primary immunodeficiency and autoimmunity: lessons from human diseases. *Scand J Immunol* **71**:317–28.

Department of Health (2008). *Clinical Guidelines for Immunoglobulin Use*, 2nd edn. London: Department of Health. Available at: [www.dh.gov.uk/en/index.htm](http://www.dh.gov.uk/en/index.htm).

Gaspar, HB, Gilmour, KC (2001). Severe combined immunodeficiency – molecular pathogenesis and diagnosis. *Arch Dis Child* **84**:169–73.

Johnston SL (2008). Clinical immunology review series: an approach to the patient with recurrent superficial abscesses. *Clin Exp Immunol* **152**:397–405.

National Blood Service, NHS Blood and Transplant (2007). *Investigation and clinical management of suspected reactions to IgA*. Available at: [http://hospital.blood.co.uk/library/doc/SPN\\_DDR\\_RC\\_019\\_03\\_IgA.doc](http://hospital.blood.co.uk/library/doc/SPN_DDR_RC_019_03_IgA.doc) (accessed on 22 October 2011).

Notarangelo LD. Primary immunodeficiencies (PIDs) presenting with cytopenias. *Hematol Am Soc Hematol Educ Program* 2009:139–43.



Oliveira JB, Fleisher TA (2010). Laboratory evaluation of primary immunodeficiencies. *J Allergy Clin Immunol* **125**(suppl 2):S297–305.

Steihm ER, ed. (2004). *Immunologic Disorders in Children and Infants*, 5th edn. WB Saunders.

Wood P, Stanworth S, Burton J *et al.*, on behalf of the UK Primary Immunodeficiency Network (2007). Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. *Clin Exp Immunol* **149**:410–23.

---

# Chapter 15

## Infection Diseases

*Nigel Klein and Karyn Moshal*

---

## CONTENTS

### 1. Notification of infectious diseases

### 2. Pathogenesis of infection

### 3. Fever with focus

3.1 Central nervous system infections

3.2 Respiratory infections

3.3 Bone and joint infections

3.4 Gastrointestinal infections

3.5 Urogenital infections

### 4. Fever with no focus/prolonged fever

4.1 Bacteraemia/septicaemia

4.2 Kawasaki disease

4.3 Infective endocarditis

4.4 Toxic shock syndrome

4.5 Brucellosis

4.6 Lyme disease

4.7 Listeriosis

4.8 Leptospirosis

4.9 Cat-scratch disease

### 5. Mycobacterial infections

5.1 Tuberculosis

5.2 Atypical mycobacteria

## **6. Fungal infections**

[6.1 Cutaneous fungal infections](#)

[6.2 Candidiasis \(thrush, moniliasis\)](#)

[6.3 Aspergillosis](#)

## **7. Viral infections**

[7.1 Human immunodeficiency virus](#)

[7.2 Hepatitis](#)

[7.3 Epstein–Barr virus](#)

[7.4 Cytomegalovirus](#)

[7.5 Herpes simplex virus](#)

[7.6 Varicella-zoster virus](#)

[7.7 Parvovirus B19 \(erythema infectiosum, ‘slapped cheek’ or fifth disease\)](#)

[7.8 Roseola infantum \(exanthem subitum or HHV-6\)](#)

[7.9 Measles](#)

[7.10 Mumps](#)

[7.11 Rubella \(German measles\)](#)

[7.12 Adenovirus](#)

[7.13 Enteroviruses](#)

[7.14 Molluscum](#)

## **8. Parasitic infections**

[8.1 Toxoplasmosis](#)

[8.2 Head lice \(pediculosis capitis\)](#)

## **9. Tropical and geographically circumscribed infections**

[9.1 Malaria](#)

[9.2 Enteric \(typhoid/paratyphoid\) fever](#)

[9.3 Dengue fever](#)

[9.4 Viral haemorrhagic fevers](#)

[9.5 Hantaviruses](#)

[9.6 \*Giardia\*](#)

[9.7 Amoebiasis](#)

[9.8 Hookworm](#)

[9.9 Leishmaniasis](#)

[9.10 Schistosomiasis](#)

[9.11 Travellers’ diarrhoea](#)

## **10. New and emerging infections**

[10.1 Severe acute respiratory syndrome](#)

[10.2 West Nile virus](#)

[10.3 Avian influenza](#)

[10.4 H1N1 influenza virus: swine flu](#)

## **11. Congenital infections**

### 11.1 Diseases

## **12. Miscellaneous**

12.1 Differential diagnosis of prolonged fever

12.2 Differential diagnosis of cervical lymphadenopathy

12.3 Infections commonly associated with atypical lymphocytosis

12.4 Diseases associated with eosinophilia

12.5 Causes of hydrops fetalis

12.6 Oxazolidinones: a new class of antibiotics

12.7 Echinocandins: a new class of antifungals

12.8 Erythema multiforme

12.9 Erythema nodosum

12.10 Anthrax

12.11 Botulism

12.12 Bovine spongiform encephalopathy and new variant Creutzfeldt–Jakob disease

## **13. Further reading**

---

# Infectious Diseases

---

## 1. NOTIFICATION OF INFECTIOUS DISEASES

Doctors in England and Wales have a statutory duty to notify the local authority, usually the CCDC (Consultant in Communicable Disease Control), of cases of certain infections: this is done via the notification book in each hospital.

Notifications of infectious diseases, some of which are microbiologically confirmed, prompt local investigation and action to control the diseases.

Diseases notifiable (to Local Authority Proper Officers) under the Health Protection (Notification) Regulations 2010:

- Acute encephalitis
- Acute meningitis
- Acute poliomyelitis
- Acute infectious hepatitis
- Anthrax
- Botulism
- Brucellosis
- Cholera
- Diphtheria
- Enteric fever (typhoid or paratyphoid fever)
- Food poisoning
- Haemolytic–uraemic syndrome (HUS)
- Infectious bloody diarrhoea
- Invasive group A streptococcal disease and scarlet fever
- Legionnaires' disease
- Leprosy
- Malaria
- Measles
- Meningococcal septicaemia
- Mumps
- Plague
- Rabies

- Rubella
- Severe acute respiratory syndrome (SARS)
- Smallpox
- Tetanus
- Tuberculosis (TB)
- Typhus
- Viral haemorrhagic fever (VHF)
- Whooping cough
- Yellow fever

As of April 2010, it is no longer a requirement to notify the following diseases: dysentery, ophthalmia neonatorum, leptospirosis and relapsing fever.

## 2. PATHOGENESIS OF INFECTION

The course and outcome of any infectious disease is a function of the interaction between the pathogen and host.

### The pathogens

Human infections are caused by bacteria, viruses, fungi and parasites. However, despite the vast array of potential pathogens, only a minority have the capacity to cause infection in a human host. Many factors determine an individual organism's ability to initiate disease, but successful organisms have three essential characteristics: the ability to invade a host; the ability to travel to an environment within the host that is conducive to their propagation; and the ability to survive the host's defence mechanisms. Increasing understanding of the molecular mechanisms underlying these pathogenic events should enable the development of new treatment strategies.

### Bacterial properties important in the pathogenesis of infections

Bacterial characteristic	Function
Pili	Aid adhesion to host targets
Capsular polysaccharide	Inhibit phagocytosis
Enzyme production	Inactivate antibody, degrade host tissue
Toxin production	Lyse circulating cells
Antigen variation	Evade host defences

### The host

The essential elements of all components of the immune system are present at birth. Initially, however, the baby's circulating immunoglobulin is derived predominantly from the mother. It is only after

encountering a wide range of potential pathogens that defences fully mature to provide adequate protection in later life. Meanwhile, these children are particularly susceptible to infections.

The importance of acquiring a fully competent host defence system is illustrated clinically by the problems encountered in immunodefective individuals, e.g. primary immunodeficiencies, acquired immune deficiency syndrome (AIDS), and those receiving chemotherapy and radiotherapy. These patients not only have severe and persistent infections caused by common organisms, but are also vulnerable to a range of unusual or opportunistic pathogens. The role played by each component of the host defence system can be deduced from the nature of infections associated with specific immunological defects, many of which present in childhood.

## Immune deficiency and susceptibility to infection

The molecular basis for many primary immunodeficiencies has been established (see Chapter 14). The table below gives a broad indication of the type of infections experienced by patients with defects affecting different components of the immune system.

Immune defect	Infectious susceptibility	
Antibody	Bacteria	<i>Staphylococcus</i> , <i>Streptococcus</i> spp., <i>Haemophilus influenzae</i> , <i>Moraxella</i> ( <i>Branhamella</i> ) <i>catarrhalis</i>
Viruses	Enteroviruses	
Protozoa	<i>Giardia</i> spp.	
Cellular immunity	Bacteria	<i>Mycobacterium</i> , <i>Listeria</i> spp.
	Viruses	Cytomegalovirus (CMV), herpesvirus, measles, respiratory syncytial virus, adenovirus
	Fungi	<i>Candida</i> , <i>Aspergillus</i> spp.
	Protozoa	<i>Pneumocystis</i> spp.
Neutrophils	Bacteria	Gram +ve, Gram –ve
	Fungi	<i>Aspergillus</i> , <i>Candida</i> spp.
Complement	Bacteria	<i>Neisseria</i> , <i>Staphylococcus</i> spp.

## 3. FEVER WITH FOCUS

### 3.1 Central nervous system infections

# Meningitis and encephalitis

Encephalitis is predominantly viral in origin.

Common viral causes include:

- Enteroviruses
- Herpes simplex virus (HSV)-1 and HSV-2
- Varicella-zoster virus
- Measles
- Mumps
- Influenza

Rare causes include:

- Adenoviruses, rubella virus, Epstein–Barr virus (EBV), arenaviruses (e.g. Japanese B encephalitis), rabies virus and *Mycoplasma* spp., West Nile virus

Herpes simplex virus causes a predominantly encephalitic illness. Aciclovir dramatically reduces mortality if given early in HSV disease.

The peak incidence of viral encephalitis is in the first 6 months of life with 1 or 2 cases per 1000 children. In about 50% of cases a mild lympho-cellular pleocytosis is seen.

The most common cause of viral meningitis is enterovirus and these infections peak in summer.

Bacterial meningitis

- *Neisseria meningitidis* is the most common cause of community-acquired bacterial meningitis in the UK, with most cases being *N. meningitidis* B since the introduction of the conjugate meningococcal C vaccine.
- *Streptococcus pneumoniae* is the second most common cause
- The incidence of *Haemophilus influenzae* type b (Hib) meningitis has dropped from around 2500 cases per year to fewer than 50 per year since the introduction of the Hib vaccine
- A rare, but serious, form of bacterial meningitis is caused by *Mycobacterium tuberculosis*. This organism can affect patients of all ages and should be considered in any atypical presentation of meningitis, particularly in patients presenting with an insidious illness

**Neonatal meningitis**

In the neonatal period, group B streptococci are the predominant meningeal pathogen, followed by Gram-negative bacilli, *Strep. pneumoniae* and *Listeria monocytogenes*.

**Diagnosis of bacterial meningitis**

If meningitis is suspected, the diagnosis should be confirmed by lumbar puncture and examination of the cerebrospinal fluid (CSF).



Specific contraindications to lumbar puncture include:

- Signs of raised intracranial pressure with changing level of consciousness, focal neurological signs or severe mental impairment
- Cardiovascular compromise with impaired peripheral perfusion or hypotension
- Respiratory compromise with tachypnoea, an abnormal breathing pattern or hypoxia
- Thrombocytopenia or a coagulopathy

A lumbar puncture should also be avoided if it causes a significant delay in treatment.

Very high white cell counts of more than  $1000/\text{mm}^3$  can be seen in bacterial meningitis. There is a broad correlation between a predominance of polymorphonuclear leukocytes in the CSF and bacterial meningitis. However, lymphocytes may predominate in early or partially treated bacterial meningitis, in tuberculous meningitis and in neonates.

In bacterial meningitis, the CSF glucose level is usually low with a CSF:blood ratio  $<0.5$ , and the protein level is frequently raised to  $>0.4$  g/l. Numerous studies have now shown that, even after the administration of intravenous antibiotics, the diagnostic cellular and biochemical changes in the CSF may persist for at least 48 hours.

### **Treatment – antibiotics for bacterial meningitis**

In infants up to 3 months of age a combination of ampicillin and cefotaxime is a logical choice: cefotaxime provides cover for both neonatal and infant pathogens, and ampicillin is effective against *L. monocytogenes*.

Penicillin-resistant meningococci are emerging worldwide, as are chloramphenicol-resistant strains, but these have not yet resulted in treatment failures. Fortunately, almost all strains in the UK remain sensitive to the third-generation cephalosporins. At the moment, the routine use of vancomycin for community-acquired meningitis is not justified in the UK.

- If the cause of meningoencephalitis is unclear it is usual to start empirical treatment with aciclovir, erythromycin and cefotaxime/ceftriaxone to cover HSV, *Mycoplasma* spp. and bacteria, respectively

### **Treatment – the role of corticosteroids**

Several studies of patients with Hib meningitis have demonstrated some improvement in morbidity (deafness or neurological deficit) if corticosteroids were given either before antibiotic administration or at the same time. Data supporting the use of steroids in pneumococcal and meningococcal meningitis are lacking.

## **Complications**

- Convulsions occur in 20–30% of children, usually within 72 h of presentation
- Subdural collections of fluid are common, particularly during infancy. They are usually sterile and

rarely require aspiration

- The most common long-term complication of meningitis is sensorineural deafness. The overall rate of deafness after meningitis is less than 5%. Hearing impairment is higher in cases of pneumococcal meningitis than in meningococcal infections

## Prevention

Conjugate vaccines against Hib and group C *N. meningitidis* are routinely given in the UK as part of the primary course of immunization at 2, 3 and 4 months of age. The conjugate pneumococcal vaccine is now also part of the routine immunization schedule, and given at 2, 4 and 13 months.

## 3.2 Respiratory infections

See Chapter 22.

## 3.3 Bone and joint infections

Bacterial infections of bones (osteomyelitis) and joints (septic arthritis) should be suspected in infants of children who present with:

- Fever
- Unexplained limp and/or abnormal posture/gait and/or reluctance to use the limb
- Musculoskeletal pain, especially in the presence of local bone or joint tenderness, swelling, erythema, and complete or partial limitation of movement
- Osteomyelitis and septic arthritis may occur separately or together and may affect one or many joints, often depending on the organism and host immunity

## Osteomyelitis

This is either **haematogenous** (most common), resulting from bacterial seeding to the bone secondary to a bacteraemia, or **non-haematogenous**, which is secondary to trauma resulting in compromised bone tissue which then becomes infected. Long bones, followed by vertebrae, are the most common sites of infection.

- Most common in those aged >1 year or 3–10 years of age
- More frequent in boys than in girls
- Mild (often unnoticed) trauma causes bone compromise, allowing bacterial seeding during transient bacteraemic events and subsequent osteomyelitis
- Destruction of the growth plates can occur in neonates, but not in older children

**Acute haematogenous osteomyelitis** presents as an acute bacteraemic illness with fever and localized bone symptoms within a week.

**Subacute haematogenous osteomyelitis** has an insidious onset, over 1–4 weeks, with fewer systemic features and more pronounced localized bone signs.

**Chronic osteomyelitis** lasts for months, often as the result of an infection that has spread from a contiguous site, e.g. a fracture, or infection with an unusual organism e.g. mycobacteria.

## Organisms

*Staphylococcus aureus* is the most common organism causing osteomyelitis in the normal host, followed by streptococci. Consider *Mycobacterium tuberculosis* in patients who present with chronic or atypical osteomyelitis, as well as *Kingella kingae*, a more recently recognized pathogen.

## Organisms involved in acute haematogenous osteomyelitis

Age	Expected organism	Comments
Neonate (0–2 months)	Group B streptococcus <i>Staph. aureus</i> <i>Escherichia coli</i>	Usually affects femur or humerus Multifocal in 20–40%, Usually associated with septic arthritis
Infant (2–24 months)	<i>Staph. aureus</i> ,  <i>Strep. pneumoniae</i> Hib Group B streptococcus Group A streptococcus <i>Kingella kingae</i>	Single long-bone metaphysis affected, usually femur  Now rare Following varicella infection
Child	<i>Staph. aureus</i> <i>Streptococci</i> <i>E. coli</i> <i>Kingella kingae</i> Salmonella	As for infant
Sickle-cell anaemia	Salmonella <i>Strep. pneumoniae</i> <i>Staph. aureus</i> Gram-negative bacilli	Diaphysis rather than metaphysis affected

## Diagnosis

- Increased white cell count (inconsistent) with neutrophilia, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) – present in 92–98% of cases, but is non-specific
- Blood cultures positive in only 40–60% of cases
- Needle aspiration of periosteal space or bone or arthrocentesis if associated septic arthritis
- Tuberculin skin test if tuberculosis is suspected
- Characteristic radiological changes occur after 10–14 days with periosteal elevation and radiolucent metaphyseal lesions
- Technetium bone scan is positive within 24–48 h of infection
- Magnetic resonance imaging detects changes early in the disease

## Differential diagnosis

Malignant and benign bone tumours, e.g. Ewing sarcoma, osteosarcomas, leukaemia with bony infiltrates and bone infarcts, e.g. sickle cell disease.

## Treatment

- 4–6 weeks of intravenous antibiotics depending on the organism. The most common cause is *Staph. aureus* and should be treated with an anti-staphylococcal penicillin. Some authorities also add fusidic acid. A definitive diagnosis from bone culture at debridement is optimal. Positive blood cultures or joint fluid cultures provide useful information
- Surgery is required if dead or necrotic bone is present
- Associated septic arthritis (especially the hip) requires incision and drainage
- Subacute or chronic infections, or disease caused by atypical organisms, e.g. mycobacteria, require longer courses of antibiotics

## Complications

Serious damage to the growth plate can cause differential limb length and a limp (if leg is involved).

## Septic arthritis

- Serious pyogenic infection of the joint space
- Slightly more common than osteomyelitis
- Secondary to bacteraemia – caused by haematogenous spread
- Most common in children aged <3 years and in sexually active young women
- Usually monoarticular, except in neonates when it is often multifocal

## Clinical presentation

Characterized by fever and a swollen, painful joint. Similar to haematogenous osteomyelitis. Neonates often present with crying when changing their nappy because of the movement of the hip joint.

## Organism

- Depends on age and immune status of the child
- Infectious arthritis may be caused by viral, fungal (very rare in immunologically normal hosts, but is well documented in the premature neonatal population) or bacterial agents
- Septic arthritis implies pyogenic arthritis secondary to bacterial infections, including *Mycobacterium tuberculosis*
- Organisms are similar to those in osteomyelitis with *Staph. aureus* being the most common. Group A streptococci are also often implicated. *Neisseria* spp. should be considered
- *N. meningitidis* infection may present with acute or occasionally chronic arthritis
- *N. gonorrhoeae* infection is not uncommon in sexually active teenagers who have polyarticular septic arthritis
- *Brucella* spp. may cause chronic septic arthritis

## Differential diagnosis

- Viral infections such as rubella, mumps, parvovirus B19 and hepatitis B
- Post-infectious, reactive and immune-complex arthritides
- Intermittent polyarticular arthritis of *Borrelia burgdorferi* (Lyme disease)
- Migrating arthritis of rheumatic fever

- Connective tissue diseases
- ‘Irritable hip’ – a transient synovitis of the hip in children aged <5 years after an upper respiratory tract infection; there is mild fever and limp with minimal systemic features, a normal ESR and white cell count, and an almost full range of movement of the affected limb

## Diagnosis – clinical

- Ultrasound scan and aspiration of joint fluid for Gram staining and microbiological culture
- Look for associated osteomyelitis
- Technetium bone scan
- Computed tomography (CT) and magnetic resonance imaging (MRI) can provide useful information early in the disease
- Blood cultures will be positive in 50% of cases

## Treatment

- Antibiotic treatment depending on the organism for at least 2 weeks
- Open surgical drainage is indicated for recurrent joint effusions and for **any** case of septic arthritis of the **hip** at the time of presentation
- Needle aspiration of fluid in other joints ± washout of the joint

Septic arthritis of the hip in a child is an emergency. Immediate open drainage reduces the intra-articular pressure and avoids aseptic necrosis of the femoral head. The femoral metaphysis can be drilled during this procedure if osteomyelitis is suspected.

## 3.4 Gastrointestinal infections

See Chapter 10, Section 11.

## 3.5 Urogenital infections

See Chapter 18, Section 12.

## 4. FEVER WITH NO FOCUS/PROLONGED FEVER

### 4.1 Bacteraemia/septicaemia

## Definitions

- **SIRS** (systemic inflammatory response syndrome) is defined by the presence of two or more abnormalities in temperature, heart rate, respiratory rate and white blood count. SIRS can follow

any severe insult including infection, trauma, major surgery, burns or pancreatitis

- **Sepsis** is used to describe SIRS in the context of bacterial infection
- **Severe sepsis** is used to describe a state characterized by hypoperfusion, hypotension and organ dysfunction
- **Septic shock** is restricted to patients with persistent hypotension despite adequate fluid resuscitation, and/or hypoperfusion even after adequate inotrope or pressor support

## Microbial aetiology of sepsis

The most common organisms in childhood are:

- *Strep. pneumoniae* (decreasing because of the introduction of the pneumococcal vaccine)
- *N. meningitidis*
- Hib (drastically reduced in countries with an immunization programme)

Rarer causes of sepsis in healthy children include:

- *Staph. aureus*
- Group A streptococci
- *Salmonella* spp.

These may be associated with wound and skin infections, varicella or a history of diarrhoea, respectively.

In neonates the usual causes of sepsis are:

- Group B streptococci
- *E. coli* and other Gram-negative bacteria
- *L. monocytogenes*

In immunocompromised patients:

- Gram-negative organisms, such as *Pseudomonas aeruginosa*
- Fungi

In patients with indwelling catheters:

- Coagulase-negative staphylococci
- Enterococci

Some viruses, including herpesviruses, enteroviruses and adenoviruses, can produce diseases that may be indistinguishable clinically from bacterial sepsis, particularly in neonates and infants.

Children with chronic diseases are more susceptible to infection with specific organisms, e.g. cystic fibrosis and pseudomonal infections and sickle cell disease and salmonella infections.

# Pathophysiology of sepsis

Lipopolysaccharides from Gram-negative bacteria and a variety of other microbial products have the capacity to stimulate the production of mediators from many cells within the human host.

Tumour necrosis factor (TNF), interleukin-1 and interleukin-6 are just a few of the many inflammatory mediators reported to be present at high levels in patients with sepsis. Recently, a family of receptors has been identified capable of transducing cellular signals in response to bacteria. These are known as human toll-like receptors.

It is the cytokines and inflammatory mediators that are produced in response to microbial stimuli which stimulate neutrophils, endothelial cells and monocytes and influence the function of vital organs, including the heart, liver, brain and kidneys.

The net effect of excessive inflammatory activity is to cause the constellation of pathophysiological events seen in patients with sepsis and septic shock.

## Treatment

Successful treatment involves the administration of appropriate antibiotics, and intensive care with particular emphasis on volume replacement and inotropic and respiratory support. A number of adjuvant therapies have been investigated, but, at present, none is used routinely.

## 4.2 Kawasaki disease

- In 1967, Tomisaku Kawasaki described 50 Japanese children with an illness characterized by fever, rash, conjunctival injection, erythema and swelling of the hands and feet, and cervical lymphadenopathy
- Kawasaki disease is associated with the development of systemic vasculitis (multisystem disease affecting medium-sized muscular arteries) complicated by coronary and peripheral arterial aneurysms, and myocardial infarction in some patients
- It is the most common cause of acquired heart disease in children in the UK and the USA
- Kawasaki disease is most common in Japan, where more than 125 000 cases have been reported. The disease is also more common in Japanese and other Oriental children living abroad.
- Children aged between 6 months and 5 years are most susceptible, with peak incidence in children aged 9–11 months. Seasonal variation in the disease incidence has been reported, with the peak occurrence during the winter and spring months
- Slight male predominance (1.6:1)

## Diagnosis of Kawasaki disease

- There is no diagnostic test for Kawasaki disease, so diagnosis is based on clinical criteria
- The differential diagnosis includes toxic shock syndrome (streptococcal and staphylococcal), staphylococcal scalded-skin syndrome, scarlet fever and infection with enterovirus, adenovirus,

measles virus, parvovirus, Epstein–Barr virus, CMV, *Mycoplasma pneumoniae*, rickettsiae and *Leptospira* spp.

## Diagnostic criteria

- Fever of 5 days' duration plus four of the five following criteria:
  - Conjunctival injection
  - Lymphadenopathy
  - Rash
  - Changes in lips or oral mucosa
  - Changes in extremities
- **Or** the presence of fever and coronary artery aneurysms with three additional criteria is required for the diagnosis of 'complete' cases
- 'Incomplete' cases comprise those with fewer than the prerequisite number of criteria. Irritability is an important sign – which, although virtually universally present, is not included as one of the diagnostic criteria
- Other relatively common clinical findings in Kawasaki disease include arthritis, aseptic meningitis, pneumonitis, uveitis, gastroenteritis, meatitis and dysuria, as well as otitis. Relatively uncommon abnormalities include hydrops of the gallbladder, gastrointestinal ischaemia, jaundice, petechial rash, febrile convulsions and encephalopathy or ataxia. Cardiac complications other than coronary arterial abnormalities include cardiac tamponade, cardiac failure, myocarditis, endocardial disease and pericarditis
- Acute phase proteins, neutrophils and the ESR are usually elevated. Thrombocytosis occurs towards the end of the second week of the illness and therefore may not be helpful diagnostically. Liver function may be deranged. Sterile pyuria is occasionally observed, and also CSF pleocytosis (predominantly lymphocytes) representing aseptic meningitis

## Treatment of Kawasaki disease

Treatment of Kawasaki disease is aimed at reducing inflammation and preventing the occurrence of coronary artery aneurysms and arterial thrombosis. Patients receive aspirin and intravenous immunoglobulin (IVIG) 2 g/kg as a single dose infused intravenously. If no response a further dose of IVIG can be given. Increasingly other interventions are being used including high dose steroids or anti-TNF.

An echocardiogram is performed at 10–14 days, 6 weeks, 6 months and then at further times if an abnormality is detected.

## Cardiac complications of Kawasaki disease

- 20–40% of untreated Kawasaki disease patients develop coronary artery abnormalities
- 50% of these lesions regress within 5 years, and regression occurs within 2 years in most cases of mild coronary artery aneurysms (3–4 mm)
- The risk of these complications is markedly reduced with the use of IVIGs and other interventions



In 1993, a report from the British Paediatric Surveillance Unit (BPSU) indicated a mortality rate of 3.7% in the UK for Kawasaki disease. Current mortality rates reported from Japan are much lower at 0.14%.

## 4.3 Infective endocarditis

- Usually occurs as a complication of congenital or rheumatic heart disease or of prosthetic valves, but it can occur in children without cardiac malformations
- There is an increased risk with central lines and intravenous drug use
- Highest-risk lesions are those associated with high-velocity blood flow, e.g. ventricular septal defects, left-sided valvular lesions and systemic–pulmonary arterial communications  
Uncommon with atrial septal defects
- Vegetations occur at the site of endocardial erosion from turbulent flow

## Organisms

### Most common organisms

- Native valve:
  - *Streptococcus viridans* group (*Strep. mutans*, *Strep. sanguis*, *Strep. mitis*)
  - *Staph. aureus*
  - Enterococci (e.g. *Strep. faecalis*, *Strep. bovis*)
- Prosthetic valves:
- *Staph. epidermidis*
- *Staph. aureus*
- *Strep. viridans*

### Uncommon organisms

- *Strep. pneumoniae*, *H. influenzae*, *Coxiella burnetii* (Q fever), *Chlamydia psittaci*, *Chlamydia trachomatis* and *Chlamydia pneumoniae*, *Legionella* spp., fungi and the HACEK organisms (*Haemophilus* spp. [*H. parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*], *Actinobacillus actinomycetem comitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*)

## Clinical presentation

- Acute: fever and septicaemia
- Non-acute: more common – prolonged fever, non-specific symptoms, e.g. fatigue, myalgia, arthralgia, weight loss, or no symptoms at all
- New murmurs or changes in known murmurs, splenomegaly, neurological manifestations, e.g. emboli, cerebral abscesses (usually *Staph. aureus*), mycotic aneurysms and haemorrhage
- Cardiac failure from valve destruction
- The classic skin lesions occur late in the disease and are now rarely seen, e.g. Osler nodes (tender

nodules in pads of the fingers and toes), Janeway lesions (painless haemorrhagic lesions on soles and palms) and splinter haemorrhages (linear lesions below nails). These are caused by circulating antigen–antibody complexes

## Investigations

- At least three separate blood cultures are taken from different sites and at different times over 2 days, cultured on enriched media for >7 days. This increases the likelihood of a positive yield, as does an increased volume of blood inoculum in each blood culture bottle
- Look for raised white cell count, high ESR, microscopic haematuria
- Echocardiography – the presence of vegetations or valvular abnormalities

## Treatment

- Broad-spectrum intravenous antibiotics, e.g. penicillin and gentamicin or vancomycin and gentamicin (depending on the most likely organism), at high bactericidal levels should be started as soon as possible after the blood cultures have been taken, because delay causes progressive endocardial damage
- Treatment duration is usually 4–6 weeks, but may be shorter for fully sensitive organisms
- Surgical intervention may be required

## Prevention

- Antibiotic prophylaxis is no longer recommended for dental procedures or for patients undergoing non-dental procedures involving the upper and lower gastrointestinal (GI) tract, genitourinary tract, and upper and lower respiratory tracts

## 4.4 Toxic shock syndrome

- Syndrome of high fever, conjunctivitis, diarrhoea, vomiting, confusion, myalgia, pharyngitis and rash with rapid progression to severe, intractable shock in some cases
- Caused by exotoxins produced by *Staph. aureus*, e.g. staphylococcal enterotoxin B or C (SEB, SEC) or toxic shock syndrome toxin-1 (TSST-1) or group A streptococci, e.g. streptococcal pyrogenic exotoxin A (SPEA)
- In staphylococcal toxic shock the focus of infection is often minor, e.g. skin abrasion
- Classically occurred in the past in females using tampons
- In streptococcal toxic shock the focus is usually severe and deep-seated, e.g. fasciitis and myositis
- Superantigen mediated, i.e. causes massive, non-major histocompatibility complex-restricted, T-cell response

## Diagnostic criteria

- Fever >38.8°C

- Diffuse macular erythroderma
- Desquamation 1–2 weeks after onset, especially on palms and soles
- Hypotension
- Involvement of three or more organs – GI tract, renal, hepatic, muscle, central nervous system (CNS); mucositis, disseminated intravascular coagulation

## Diagnosis

- Clinical
- Identification of toxin or antibodies to toxin

## Treatment

- Supportive
- Intravenous antibiotics: clindamycin or linezolid
- Intravenous immunoglobulin

## 4.5 Brucellosis

- *Brucella* species (e.g. *B. abortus*, *B. melitensis*) are non-motile Gram-negative bacilli
- Zoonotic disease, transmitted to humans by ingestion of unpasteurized milk or by direct inoculation to abraded skin
- Incubation period 1–4 weeks
- Disease is often mild in children

### Acute brucellosis

- Fever, night-sweats, headaches, malaise, anorexia, weight loss, myalgia, abdominal pain, arthritis, lymphadenopathy, hepatosplenomegaly
- Complications include meningitis, endocarditis, osteomyelitis

### Chronic brucellosis

- Fevers, malaise, depression, splenomegaly

## Diagnosis

- Prolonged culture of blood, bone marrow or other tissue, paired serology

## Treatment

- Co-trimoxazole at high dose and rifampicin for 6 weeks
- Alternative regimen in children over 8 years: doxycycline and rifampicin for 6 weeks

## 4.6 Lyme disease

- Disease occurs on the east coast of the USA and in parts of Europe and the UK
- Caused by spirochaete *Borrelia burgdorferi*, transmitted by ixodes ticks
- Incubation from tick bite to erythema migrans is 3–31 days

### Clinical manifestations

There are three stages:

- **Early localized** – distinctive rash (bull's eye lesion) – erythema migrans – red macule/papule at site of tick bite, which expands over days/weeks to large annular erythematous lesion with partial clearing, approximately 15 cm in diameter. Associated with fever, malaise, headache, neck stiffness
- **Early disseminated** – 3–5 weeks after bite – multiple erythema migrans, cranial nerve palsies especially cranial nerve VII, meningitis, conjunctivitis, arthralgia, myalgia, headache, malaise, rarely carditis
- **Late disease** – recurrent arthritis, pauciarticular, large joints, neuropathy, encephalopathy

### Diagnosis

- Clinical
- Serology and immunoblotting to detect production of antibodies to *B. burgdorferi* can be problematic because they are negative in early disease and, once present, persist beyond resolution of disease
- Polymerase chain reaction (PCR) amplification – currently a research tool only

### Treatment

- Doxycycline for child >8 years (avoid sun exposure), or amoxicillin if <8 years for 14–21 days if early disease, 21–28 days if disseminated or late disease
- Intravenous ceftriaxone or intravenous penicillin if meningitis, encephalitis, carditis or recurrent arthritis

## 4.7 Listeriosis

- Caused by *Listeria monocytogenes*, a Gram-positive bacillus
- Variable incubation of 3–70 days
- Isolated from a range of raw foods, including vegetables and uncooked meats, as well as processed foods and soft cheeses and meat-based pâtés
- Most cases are believed to be food borne. Some cases are the result of direct contact with animals.

Mother-to-fetus transmission *in utero* or during birth or via person-to-person spread between infants shortly after delivery

- Unborn infants, neonates, immunocompromised individuals, pregnant women and elderly people are at high risk

## Clinical manifestations

- Influenza-like illness or meningoencephalitis/septicaemia; spontaneous abortion
- Maternal infections can be asymptomatic

## Treatment

- Ampicillin

## 4.8 Leptospirosis

- This is a spirochaetal disease caused by *Leptospira* spp.
- Many wild and domestic animals, e.g. rats, dogs and livestock, harbour and excrete *Leptospira* spp. in their urine
- Transmission is by direct contact of mucosal surfaces or abraded skin with urine or carcasses of infected animals; or by indirect contact, e.g. swimming in water contaminated by infected urine
- Incubation period is 1–2 weeks

## Clinical manifestations

- This is an acute febrile illness that can be biphasic. The initial phase is septicaemic in nature and varies in severity from a mild self-limited illness to life-threatening disease. The initial illness lasts 3–7 days. Clinically, there is abrupt onset with fevers, rigors, headaches, myalgia, malaise and conjunctival injection
- Recovery can then be followed, a few days later, by an immune-mediated disease. Clinical presentation includes fever, aseptic meningitis, uveitis, myalgias, lymphadenopathy and vasculitis rashes
- 90% will be anicteric; however, 10% will be severely unwell with jaundice, renal dysfunction, respiratory, cardiac and CNS disease. There is a case fatality rate of 5–40% in this group

## Diagnosis

- Blood and CSF culture in the first 10 days of illness and urine after 1 week. Yield is low, the incubation period is prolonged and special culture media are required
- Serology, although retrospective, is the most reliable diagnostic tool
- PCR is useful for early diagnosis but is available in a only few laboratories

## Treatment

- Intravenous penicillin for severe disease
- Oral doxycycline (if child is >8 years old) or oral amoxicillin if child <8 years for mild disease

## 4.9 Cat-scratch disease

- Caused by *Bartonella henselae* – a fastidious Gram-negative bacterium
- Organism transmitted between cats by the cat flea. Humans are incidental hosts. There is no person-to-person spread
- More than 90% of patients have a history of contact with cats (usually kittens)

### Clinical manifestations

- Fever and mild systemic symptoms occur in 30% of patients
- A skin papule is often found at the site of presumed bacterial inoculation
- Predominant sign is regional lymphadenopathy, involving the nodes that drain the site of inoculation
- In up to 30% of cases the lymph node will suppurate spontaneously

### Complications

- Encephalitis, aseptic meningitis, neuroretinitis, hepatosplenic microabscesses and chronic systemic disease occur occasionally but are more common in the immunocompromised patient

### Diagnosis

- Immunofluorescence antibody assays are the most useful diagnostic tests
- PCR is available in some laboratories but is not recommended
- Histology of the lymph node and staining with Warthin–Starry silver stain may show characteristic necrotizing granulomas and/or the causative organism

### Treatment

- Most disease is self-limiting so treatment is symptomatic
- For those who are severely unwell and for immunocompromised patients, antibiotics such as ciprofloxacin, rifampicin, azithromycin and intravenous gentamicin are used

## 5. MYCOBACTERIAL INFECTIONS

### 5.1 Tuberculosis

- Disease caused by infection with *Mycobacterium tuberculosis*, an acid-fast bacillus
- Incubation period, i.e. infection to development of positive tuberculin skin test, is 2–12 weeks

(usually 3–4 weeks)

- Incidence is increasing again in the UK (especially in immigrant patients and those with human immunodeficiency virus [HIV])
- Host (immune status, age, nutrition) and bacterial (load, virulence) factors determine whether infection progresses to disease. Defects in interferon- $\gamma$  and interleukin-12 pathways predispose to infection
- Children usually have primary TB, adults may have either new infections or reactivation disease
- Children are rarely infectious
- Children are usually infected by an adult with ‘open’, i.e. sputum-positive pulmonary TB, so notification and contact tracing are essential
- Approximately 30% of healthy people closely exposed to TB will become infected, of whom only 5–10% will go on to develop active disease. Young children exposed to TB are more likely to develop disease than healthy adults
- Risk of disease is highest in the first 6 months after infection

### **TB exposure:**

- Patient exposed to person with contagious pulmonary TB
- Clinical examination, chest radiograph and Mantoux negative
- Some will have early infection, not yet apparent

### **TB infection:**

- Positive Mantoux test
- Asymptomatic with normal clinical examination
- Chest radiograph normal
- Treat with chemoprophylaxis

### **TB disease:**

- Positive Mantoux test
- Clinical symptoms/signs of TB, and/or
- Chest radiograph signs consistent with TB
- Treat with chemotherapy

## **Pathogenesis**

- Majority of infections are acquired via the respiratory route, occasionally ingested
- Organisms multiply in periphery of the lung and spread to regional lymph nodes, which may cause hilar lymphadenopathy
- Pulmonary macrophages ingest bacteria and mount a cellular immune response
- In most children, this primary pulmonary infection is controlled by the immune system over 6–10 weeks. Healing of the pulmonary foci occurs, which later calcifies (Ghon focus). Any surviving bacilli remain dormant but may reactivate later in life and cause tuberculous disease which can be

smear positive and contagious

## **Clinical symptoms/signs**

TB infection – usually asymptomatic, may develop fever, malaise, cough or hypersensitivity reactions – erythema nodosum or phlyctenular conjunctivitis.

## **Clinical signs=disease**

- Progressive primary pulmonary TB: foci of infection not controlled but enlarge to involve whole middle and/or lower lobes, often with cavitation (look for immunodeficiency) – fever, cough, dyspnoea, malaise, weight loss
- Dissemination to other organs (especially in children aged <4 years):
  - Miliary TB – acutely unwell, fever, weight loss, hepatosplenomegaly, choroidal tubercles in retina, miliary picture on chest radiograph
  - TB meningitis (see Section 3.1)
  - TB pericarditis – fever, chest pain, signs of constrictive pericarditis
  - Bone and joint infection
  - Urogenital infection (very rare in childhood)
  - Gastrointestinal tract – abdominal pain, malabsorption, obstruction, perforation, fistula, haemorrhage, ‘doughy’ abdomen (usually ingested rather than disseminated)

## **Congenital TB**

See Section 11.

## **Neonatal contact for mother with TB**

Infant is at high risk of acquiring TB. Evaluate mother and child (with clinical examination and chest radiograph).

- If mother is ‘smear positive’ or has an abnormal chest radiograph, separate neonate and mother until both are on adequate medication and mother is non-contagious
- If congenital TB is excluded, give 3 months of prophylactic isoniazid
- At 3 months, perform a Mantoux test:
  - If this is negative and a repeat chest radiograph is negative then give BCG (bacille Calmette–Guérin) and stop chemoprophylaxis
  - If it is positive reassess for TB disease – if there is no disease continue isoniazid for another 3 months; if disease is present then treatment with triple or quadruple therapy is required

## **Diagnosis**

### *Tuberculin tests*

Tuberculin tests involve an intradermal test of delayed hypersensitivity to tuberculin purified-protein derivative (PPD).



- **Mantoux test** – dose in UK is 0.1 ml of 1:1000, i.e. 10 tuberculin units (use 1:10 000 if risk of hypersensitivity, e.g. erythema nodosum or phlyctenular conjunctivitis). Mantoux tests are more accurate than Heaf tests and should be used for all patients where disease is suspected and for contact tracing. Measure induration, not erythema, at 48–72 h. Interpretation is difficult but test is positive if:
  - >15 mm induration in anyone (equivalent to Heaf 3–4)
  - >5–14 mm induration (equivalent to Heaf 2) if not had BCG and at high risk, e.g. found at contact or new immigrant screening, or in child aged <4 years
  - **Note** that a negative Mantoux test does **not** exclude a positive diagnosis – the test may be negative if it was incorrectly inserted; if anergy is present (in 10% of the normal population and also occurs in very young children), if there is overwhelming disseminated TB and in some viral infections, e.g. HIV, measles, influenza
- **Heaf test** – used for mass screening only. If positive refer to TB clinic. Positive is grade 2–4 if no previous BCG, grade 3 or 4 if BCG received previously. This is not an appropriate test for contact tracing, and not as accurate as a Mantoux test
- **IGRA (interferon- $\gamma$  release assays)** – these are increasingly being used. They are tests in which blood is incubated with TB antigens and the interferon- $\gamma$  is then measured. They give a similar level of detection to Mantoux tests. The combination of using both tests improves diagnosis by around 15% over each test alone

## Microbiological tests

- Ziehl–Neelsen stain for acid-fast bacilli, and culture for 4–8 weeks of sputum, gastric washings, bronchoalveolar lavage fluid, CSF, biopsy specimens (culture is required because it will provide details of type and sensitivities)
- All have low yield in children because there are lower numbers of bacteria

## Other

- **Histology** – caseating granuloma and acid-fast bacilli
- **PCR** – poor sensitivity and specificity at present but improving
- **Chest radiograph** – typical changes of hilar lymphadenopathy  $\pm$  parenchymal changes

## Treatment

### Chemoprophylaxis

Chemoprophylaxis is required:

- For those with TB infection (i.e. a positive Mantoux test, well child, normal chest radiograph) to prevent progression to disease
- For close contacts of smear-positive TB patients if they are HIV positive or immunosuppressed patients because they may not develop a positive Mantoux response

Options for chemoprophylaxis are:

- Isoniazid for 6 months (+ pyridoxine for breastfed infants and malnourished infants)
- **Or** isoniazid and rifampicin for 3 months

A repeat chest radiograph at the end of treatment is not required if there has been good compliance and the child is asymptomatic.

## Chemotherapy

For those with signs of disease four drugs are used in the initial 2 months of treatment because of the increase in isoniazid resistance (now over 7% in London, UK). The fourth drug (usually ethambutol/streptomycin) can be **omitted** if there is a **low** risk of isoniazid resistance, i.e. previously untreated, white, proven or suspected HIV-negative patients, or those who have had **no** contact with a TB patient with drug resistance.

- Pulmonary and non-pulmonary disease (except meningitis) – isoniazid and rifampicin for 6 months with pyrazinamide and a fourth drug for the first 2 months
- Meningitis – 12 months' total therapy with isoniazid and rifampicin, with pyrazinamide and a fourth drug for the first 2 months
- Multidrug-resistant TB (1% of all cases) – seek expert advice
- **Note** that directly observed therapy is recommended if there is any chance of non-compliance
- Corticosteroids should be used for 6–8 weeks if there is TB meningitis, pericarditis, miliary TB and endobronchial disease with obstruction, but only **with** anti-TB therapy

## Prevention

- Improvement of social conditions and general health
- BCG immunization (live attenuated strain of *Mycobacterium bovis*) gives approximately 50% protection. It is effective in the prevention of extrapulmonary disease in the age group <4 years. In the UK, BCG is given at birth to high-risk groups and at 12–14 years of age to tuberculin test-negative children

## Complications of BCG immunization

Include subcutaneous abscess, suppurative lymphadenitis and disseminated disease in severely immunocompromised children.

## 5.2 Atypical mycobacteria

- Infections caused by non-tuberculous mycobacteria, e.g. *Mycobacterium avium* complex, *M. scrofulaceum*, *M. kansasii*
- Ubiquitous organisms – found in soil, food, water and animals
- Found worldwide
- Acquired via ingestion, inoculation or inhalation of organism
- Many people exposed, but only a small number have infection or disease

- May cause disseminated disease in immunodeficient patients, e.g. HIV positive

## Clinical presentations

- Lymphadenitis (usually cervical), pulmonary infections, cutaneous infections and occasionally, osteomyelitis

## Diagnosis

- Isolation and identification by culture (PCR in some laboratories)
- May have weakly positive Mantoux test (with no signs of TB)

## Treatment

- For non-tuberculous mycobacterial lymphadenitis – surgical excision alone
- If excision is incomplete, or other site is involved, medical treatment with at least two drugs for 3–6 months is required

**Note** that for differential diagnosis of persistent cervical lymphadenopathy, see Section 12.2.

## 6. FUNGAL INFECTIONS

- Many fungi are ubiquitous, growing in soil, decaying vegetation and animals
- Infection is acquired by inhalation, ingestion and inoculation from direct contact
- Often produce spores
- Superficial infections are common
- Invasive disease occurs almost exclusively in immunocompromised people, mainly those with neutrophil defects or neutropenia. Consider if a neutropenic patient is not responding to antibacterial therapy after 48 h of illness

### 6.1 Cutaneous fungal infections

#### Tinea versicolor or pityriasis versicolor

- Caused by *Malassezia furfur* (*Pityrosporum orbiculare*)
- Oval, macular lesions on neck, upper chest, back, arms; may be hypo- or hyperpigmented
- Diagnosis by microscopy of skin scrapings
- Treatment with topical antifungals and salicylic acid preparations

#### Ringworm (dermatophytoses)

These are caused by filamentous fungi belonging to three main genera – *Trichophyton*, *Microsporum*

and *Epidermophyton* – diagnosed by skin scrapings.

### **Tinea capitis (ringworm of scalp)**

- Causes patchy dandruff-like scaling with hair loss, discrete pustules or kerion – boggy, inflammatory mass  $\pm$  fever and local lymphadenopathy
- Treat with oral antifungals, e.g. griseofulvin, terbinafine. Topical agents not effective

### **Tinea corporis (ringworm of body)**

- Usually dry, erythematous annular lesion with central clearing, on face, trunk and limbs
- Treat with topical antifungals for 4 weeks; if no response use oral antifungals

### **Tinea cruris (jock itch!)**

- Infection of groin and upper thighs causing itchy erythematous, scaly skin
- Treat as tinea corporis

### **Tinea pedis (athlete's foot)**

- Infection in interdigital spaces, may involve the whole foot. Fungi are common in damp areas, e.g. swimming pools. Treat as tinea corporis

## **6.2 Candidiasis (thrush, moniliasis)**

- Usually caused by *Candida albicans*
- Present on skin, in the mouth, and in the GI tract and vagina of healthy individuals
- Person-to-person transmission occurs
- Use of antibiotics may promote overgrowth of yeasts

### **Clinical manifestations**

#### **Mild mucocutaneous infection**

- Oral thrush and/or nappy-area dermatitis are common in infants
- Vulvovaginal candidiasis occurs in adolescents
- Intertriginous lesions, e.g. in neck, groin, axilla

#### **Chronic mucocutaneous candidiasis**

- Associated with endocrine disease and progressive T-cell immunodeficiencies

#### **Invasive disease**

- Disseminated disease to almost any organ, especially in very low-birthweight newborns and those who are immunocompromised

## Diagnosis

- Microscopy showing pseudohyphae or germ-tube formation (*C. albicans* only)
- Culture

## Treatment

- For minor mucocutaneous disease, use oral nystatin or topical nystatin/clotrimazole/miconazole
- For severe or chronic mucocutaneous disease, use an oral azole, e.g. fluconazole
- For invasive disease, treat as for aspergillus infection (see below)

## 6.3 Aspergillosis

- Caused by *Aspergillus fumigatus*, *A. niger*, *A. flavus* and, rarely, others
- No person-to-person transmission

## Clinical manifestations

- Allergic bronchopulmonary aspergillosis – episodic wheezing, low-grade fever, brown sputum, eosinophilia, transient pulmonary infiltrates. Usually in children with cystic fibrosis or asthma. Treat with steroids
- Sinusitis and otomycosis of external ear canal – usually benign in immunocompetent patients
- Aspergilloma – fungal balls that grow in pre-existing cavities or bronchogenic cysts – non-invasive
- Invasive aspergillosis – extremely serious
- May cause peripheral patchy bronchopneumonia with clinical manifestations of acute pneumonia
- Often disseminates to brain, heart, liver, spleen, eye, bone and other organs in the immunocompromised patient population

## Diagnosis

- High clinical index of suspicion
- Microscopy shows branched and septate hyphae
- Culture
- Molecular testing is useful but availability is limited

## Treatment

- For invasive disease treatment with two agents is now often used: liposomal amphotericin in high dose or voriconazole and a second antifungal, e.g. an echinocandin, an azole or flucytosine depending on culture results

- Surgical excision of localized lesion

## 7. VIRAL INFECTIONS

### 7.1 Human immunodeficiency virus

- HIV is a retrovirus, i.e. it contains the enzyme reverse transcriptase, which allows its viral RNA to be incorporated into host-cell DNA
- Two main types are known: HIV-1 (widespread) and HIV-2 (West Africa)
- Mainly infects CD4 helper T cells, causing reduction of these cells and acquired immunodeficiency

### Transmission

- Vertical (most common mode of transmission in children):
  - Prenatal
  - Intrapartum (most common)
  - Postnatally via breast milk
- Blood or blood products, e.g.
  - People with haemophilia (of historical interest only in the UK now)
  - Non-sterile needle use
- Via mucous membranes, e.g. sexual intercourse (**note** sexual abuse)

### Diagnosis

- Virus detection by PCR (rapid, sensitive, specific)
- Detection of immunoglobulin G (IgG) antibody to viral envelope proteins (gp120 and subunits)

Diagnosis of HIV infection if:

- HIV antibody-positive after 18 months old if born to an infected mother, or at any age if mother is not infected – on two occasions
- PCR positive on two separate specimens taken at different times

Babies of HIV-positive mother:

- Start zidovudine (AZT, azidothymidine) orally for baby within 12 h of birth. This is continued for 4 weeks:
  - 24–48 h – HIV PCR (50% true positive by 1 week, 90% by 2 weeks)
  - 6 weeks – repeat HIV PCR, start Septrin prophylaxis
  - 3–4 months – repeat HIV PCR
- If all three PCRs are negative then >95% chance baby is **not** infected
- Stop Septrin
- Follow up until HIV antibody (vertically acquired from mother) is negative

- **Note** that still HIV affected, i.e. many issues re infection in family

Follow-up of HIV-positive babies/children:

- Every 3–6 months depending on health
- History and examination for signs of persistent or unusual infections and growth/puberty
- Psychological and social support, issues re awareness of diagnosis
- Full blood count, T-cell subsets/CD4 count, HIV viral load
- Hepatitis B and C viruses, CMV, toxoplasma status if indicated
- Immunization information
- Septrin prophylaxis is continued for the first year of life in all HIV-positive children regardless of CD4 count:
  - All infants under the age of 24 months require triple antiretroviral treatment
  - All children between 2 and 5 years with a CD4 count  $<25\%$  or absolute count  $<750$  cells/mm<sup>3</sup> require antiretroviral treatment
  - All children  $>5$  years with an absolute CD4 count  $<350$  cells/mm<sup>3</sup> require treatment
  - Children who fulfil the clinical criteria for treatment should be given antiretroviral treatment regardless of their CD4 counts

## WHO clinical staging

### Clinical stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

### Clinical stage 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
- Fungal nail infections

### Clinical stage 3

- Unexplained moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)

- Unexplained persistent fever (above 37.5°C, intermittent or constant, for >1 month)
- Persistent oral candidiasis (after first 6 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymph node TB
- Pulmonary TB
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anaemia ( $<8.0$  g/dl), neutropenia ( $<0.5 \times 10^9/l$ ) or chronic thrombocytopenia ( $<50 \times 10^9/l$ )

## Clinical stage 4

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration, or visceral at any site)
- Extrapulmonary TB
- Kaposi sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- CNS toxoplasmosis (after the neonatal period)
- HIV encephalopathy
- CMV infection; retinitis or CMV infection affecting another organ, with onset at age >1 month
- Extrapulmonary cryptococcosis including meningitis
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacterial infection
- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- HIV-associated cardiomyopathy or nephropathy

All children who fulfil stages 3 and 4 clinical criteria require triple antiretroviral therapy regardless of their CD4 counts.

- 1997 – 20% of vertically infected children developed AIDS in infancy; most common AIDS-defining illness was *Pneumocystis jiroveci* pneumonia
- 2001 – improved antenatal detection and prophylaxis, therefore fewer AIDS-defining illnesses in infancy
- Approximately 5% of children with HIV develop AIDS each year



## Recurrent bacterial infections

- B-cell dysregulation occurs, despite often high immunoglobulin levels, because of poor CD4 (T-helper cell) function
- Recurrent serious bacterial infections, such as pneumonia, meningitis, septicaemia and osteomyelitis, may occur. The most common organisms are those that are normally pathogenic, *Strep. pneumoniae*, *H. influenzae*, coliforms and *Salmonella* spp.
- Treatment depends on clinical condition and probable infective organism

## Faltering growth

This is frequently multifactorial, e.g.:

- Reduced nutrient and fluid intake – psychosocial reasons or oral and oesophageal thrush
- Increased nutrient and fluid requirement with chronic disease (30–50%)
- Increased fluid loss with diarrhoea – look for gut pathogens, microsporidiosis, cryptosporidiosis, *Giardia* spp., atypical mycobacteria and viruses
- **Treatment:** improve immune function with highly active antiretroviral therapy (HAART); treat specific infections; provide dietary supplements

## Lymphocytic interstitial pneumonitis

- Caused by diffuse infiltration of pulmonary interstitium with CD8 (cytotoxic) lymphocytes and plasma cells
- Often diagnosed from a chest radiograph in an otherwise asymptomatic child
- May cause progressive cough, hypoxaemia and clubbing
- Associated with parotitis
- Superimposed bacterial infections and bronchiectasis may occur
- May have element of reversible bronchoconstriction
- **Treatment:** symptomatic; HAART; if severe use oral prednisolone

## HIV encephalopathy

- May present with regression of milestones, behavioural difficulties, acquired microcephaly, motor signs, e.g. spastic diplegia, ataxia, pseudobulbar palsy
- Exclude CNS infections and lymphoma
- Treatment: HAART

## Thrombocytopenia

- Not associated with other indicators of disease progression
- **Treatment:** only if symptomatic or platelet count persistently  $<20\,000/\text{mm}^3$ . Options include intravenous immunoglobulin, steroids, HAART or last-resort splenectomy (not recommended)

because it further increases the risk of sepsis)

## Opportunistic infections

### Protozoa

- *Pneumocystis jiroveci* pneumonia  $\pm$  CMV pneumonitis:
  - Most common at 3–6 months of age; presents with persistent non-productive cough, hypoxaemia, dyspnoea, minimal chest signs on auscultation
  - Chest radiograph shows bilateral perihilar ‘butterfly’ shadowing; diagnosis by bronchoalveolar lavage; ensure no concurrent CMV infection
  - **Treatment:** supportive, may need to be treated in paediatric intensive care unit. High-dose co-trimoxazole (Septrin) for 21 days together with steroids. Intravenous aciclovir if there is concurrent CMV disease. Once stable, commence HAART. Prophylactic low-dose Septrin after treatment
- Cerebral toxoplasmosis:
  - Rare in childhood HIV infection; may present with focal signs  $\pm$  fits
  - CT shows multiple intraparenchymal ring-enhancing lesions. Positive toxoplasmosis serology
  - **Treatment:** 6 weeks of pyrimethamine and sulfadiazine with folinic acid and HAART
- Cryptosporidiosis:
  - *Cryptosporidium parvum* causes severe secretory diarrhoea, abdominal pain and sometimes sclerosing cholangitis
  - Diagnosis by stool microscopy  $\pm$  small-bowel biopsy
  - **Treatment:** supportive, paromomycin

### Fungi

- *Candida albicans* – oropharyngeal, oesophageal, vulvovaginal, disseminated (rare):
  - **Treatment:** chronic antifungal therapy, e.g. fluconazole, voriconazole, intravenous liposomal amphotericin B if severe
- *Cryptococcus neoformans* – meningitis (insidious onset), pneumonia:
  - Diagnosis by CSF examination (Indian ink stain, antigen, culture), serum culture, antigen
  - **Treatment:** fluconazole. In severe disease, two antifungal agents should be used

### Viruses

- CMV – retinitis, colitis, pneumonitis, hepatitis, pancreatitis:
  - Diagnosis by serum PCR, immunofluorescence in relevant sample and characteristic retinal changes if present; differentiate disease from carriage
  - **Treatment:** intravenous ganciclovir; HAART
- Herpes simplex virus:
  - Types 1 and 2 – extensive oral ulceration
  - **Treatment:** intravenous aciclovir, oral prophylaxis if recurrent and severe; HAART may help
- Measles, varicella-zoster virus, respiratory syncytial virus, adenovirus – all may cause severe disease in HIV-infected children, especially pneumonitis

## TB and atypical TB

- Increased risk of TB and atypical TB, especially disseminated *M. avium* complex
- See Section 5

## Tumours

These are rare in children.

- Kaposi sarcoma – tumour of vascular endothelial cells, associated with human herpesvirus-8 (HHV-8); involves skin, gut, lung and lymphatics:
  - **Treatment:** HAART, local radiotherapy, chemotherapy if disseminated
- Lymphoma – non-Hodgkin B-cell primary CNS lymphoma:
  - Focal neurological signs  $\pm$  fits; CT shows single lesion
  - Definitive diagnosis by brain biopsy
  - **Treatment:** radio-/chemotherapy; poor prognosis

## HIV treatment

### Highly active antiretroviral therapy

When to start treatment in children differs in each country.

In the UK, start treatment if there is an AIDS-defining illness, or the child fulfils stage 3 or 4 WHO clinical criteria or has a rapidly decreasing CD4 count.

All children aged <2 years should be started on treatment regardless of CD4 count (CHER Study); children aged 2–5 years require treatment if CD4 count <25% or absolute count <750 cells/mm<sup>3</sup> and all children aged >5 years with CD4 count <350 cells/mm<sub>3</sub> require treatment.

- Three-drug therapy is the gold standard. This reduces resistance and suppresses viral load to undetectable levels
- The standard HAART regimen comprises a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) and **either** a non-NRTI **or** a protease inhibitor. Tenofovir, a nucleotide reverse transcriptase inhibitors, can be used interchangeably with the NRTIs in the backbone of the regimen. Liaise with the tertiary centre for any treatment decisions
- Monitor for efficacy (viral load and CD4 count) and side effects

### *P. jiroveci* prophylaxis

- For first 12 months of life if vertically infected
- If CD4 count <15%

### Reduction of vertical transmission

With breast-feeding and no intervention vertical transmission rate is 15–30%.

Interventions:

- No breast-feeding (where safe alternative is possible): transmission rate is 15%
- + antiretrovirals to mother and baby, e.g. ACTG O76 trial – reduces rate to 5%
- + elective caesarean section – reduces transmission to 2% (or less if very low maternal viral load)

To allow intervention, women need to be diagnosed before giving birth. National targets and objectives were set in 1999 that involve the offer and recommendation of an HIV test to all pregnant women throughout the UK. By 2001 80% of maternity units in the UK offered this service, with an uptake of approximately 70%.

Some units now favour vaginal delivery for women who have had uncomplicated deliveries in the past, and are well controlled on treatment with good CD4 counts and undetectable viral loads.

**Note** that, if vaginal delivery, avoid invasive fetal procedures, e.g. fetal blood sampling.

There are five classes of antiretroviral drugs:

- Nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors
- Integrase inhibitors
- CCR5 receptor blockers

The last two classes of drugs are not used as standard for children, and studies are still being run to determine dosages, efficacy and side effects in children. They are being used for very drug-experienced adolescents where other treatment options have been exhausted.

Combined drug preparations are available for older children and adults. Fixed drug combination tablets are available in the developing world setting, but not in the UK.

## Major side effects of commonly used antiretroviral drugs used in children

Drug	Side effect
<i>Nucleoside reverse transcriptase inhibitors</i>	
AZT – zidovudine	Nausea, bone marrow suppression, myopathy
DDI – didanosine	Peripheral neuropathy, pancreatitis function test
3TC – lamivudine	Rare – peripheral neuropathy, pancreatitis
Abacavir	Life-threatening hypersensitivity reactions – usually present as rash and fever
D4T – stavudine (rarely used)	Peripheral neuropathy, pancreatitis, elevation of liver
<i>Non-nucleoside reverse</i>	

## *transcriptase inhibitors*

Efavirenz	Rash, sleep disturbances, hallucinations (rare in children)
Nevirapine	Rash, hepatitis

## *Protease inhibitors*

Ritonavir	Gastrointestinal side effects common in first 4 weeks, paraesthesia
Kaletra (lopinavir boosted with ritonavir)	Raised transaminases
Atazanavir	Jaundice, rarely psychosis

---

**Note** that protease inhibitors and D4T are associated with lipodystrophy.

## 7.2 Hepatitis

See Chapter 13.

## 7.3 Epstein–Barr virus

This causes infectious mononucleosis (glandular fever). EBV infects pharyngeal epithelial cells and then B lymphocytes. These disseminate and proliferate until checked by activated T cells.

- **Transmission:** saliva, aerosol
- **Incubation:** 30–50 days
- **Clinical presentation:**
  - Fever, sore throat, lymphadenopathy, palatal petechiae and malaise
  - Splenomegaly (50%), hepatomegaly (30%), hepatitis (80%), clinical jaundice (5%), thrombocytopenia, haemolytic anaemia
  - Maculopapular rash (5–15%), 90% if given ampicillin
- **Complications:**
  - Meningitis, encephalitis, Guillain–Barré, syndrome, myocarditis, splenic rupture, airway obstruction from pharyngotonsillar swelling
  - Chronic fatigue-like syndrome
  - Disseminated disease with B-cell proliferation in those with T-cell immunodeficiencies
- **Diagnosis:** atypical lymphocytosis, positive Paul–Bunnell (often negative in young children) or Monospot test, serology, heterophile antibodies, PCR
- **Treatment:** supportive, steroids for severe inflammatory processes

## 7.4 CYTOMEGALOVIRUS

- **Transmission:** close contact, blood, organ transplantation
- **Clinical presentation:**
  - In normal hosts – often asymptomatic or glandular fever-like picture
  - In immunocompromised patients – severe disease may occur with pneumonitis, retinitis, encephalitis, hepatitis and GI disturbance
  - CMV is the most common congenital infection
- **Diagnosis:** immunofluorescence, intranuclear inclusions in biopsy specimens, culture, detection of early antigen fluorescence foci (DEAFF) test, PCR
- **Treatment:** symptomatic, intravenous ganciclovir and/or intravenous foscarnet if immunosuppressed. An oral drug, valganciclovir, has been introduced and may be used instead of intravenous therapy. Its use is still being evaluated.

## 7.5 Herpes simplex virus

- **Infection:** two types recognized: HSV-1 (usually infects skin and mucous membranes) and HSV-2 (usually genital):
  - Primary infections – 85% subclinical
  - Recurrent infections – reactivation of latent infection
- **Incubation:** 2–12 days
- **Transmission:** direct contact. Congenital infections occur in approximately 1:10 000 live births in the UK. They can present as localized infection, disseminated infection or neonatal encephalitis
- **Clinical presentation:**
  - Acute herpetic gingivostomatitis – primary infection – acute painful mouth ulcers and fever, most common between 1 and 3 years of age, self-limiting, lasts 4–9 days (may be asymptomatic)
  - Recurrent stomatitis – localized vesicular lesions in nasolabial folds, ‘cold sores’
  - Keratoconjunctivitis and corneal ulcers
  - Meningoencephalitis (peak incidence in the neonatal group and in adolescence)
  - Eczema herpeticum – widespread infection of eczematous skin with HSV vesicles – may be very severe
  - Genital lesions – usually in sexually active adolescents (**note** child abuse)
  - Neonatal HSV – usually from vaginal secretions at delivery – high morbidity and mortality
- **Diagnosis:**
  - Clinical, electron microscopy of vesicular fluid (very fast), PCR, culture (this is a fast-growing virus and cultures can be positive within 2–5 days)
- **Treatment:**
  - Aciclovir – intravenous if severe disease, immunocompromised, neonate or eczema herpeticum
  - Oral, topical, eye drops

## 7.6 Varicella-zoster virus

This produces chickenpox (varicella) as a primary infection. Shingles (herpes zoster) is caused by reactivation of dormant varicella-zoster virus (VZV) from dorsal root or cranial ganglia. You can

catch chickenpox from contact with chickenpox **or** shingles. You cannot 'catch' shingles.

## Chickenpox

- **Incubation:** chickenpox: 11–24 days
- **Transmission:** direct contact, droplet, airborne; infectious from 24 h before rash appears until all spots have crusted over (approximately 7–8 days)
- **Clinical presentation:** prodrome of fever and malaise for 24 h; rash appears in crops, papular then vesicular and itchy, usually start on trunk and spread centripetally; crops continue to appear for 3–4 days and each crusts after 24–48 h. Household contacts, who receive a higher viral inoculum, tend to have more severe disease
- **Complications:**
  - Secondary bacterial infection often with group A streptococci
  - Thrombocytopenia with haemorrhage into skin
  - Pneumonia
  - Purpura fulminans
  - Post-infectious encephalitis
  - Immunocompromised patients – severe disseminated haemorrhagic disease
- **Diagnosis:** clinical, viral culture, serology and immunofluorescence assay, PCR
- **Treatment:** supportive; intravenous aciclovir for immunosuppressed or severely unwell patient
- **Prophylaxis:** zoster immunoglobulin (ZIG) if high risk (e.g. immunodeficiency, immunosuppressive treatment). **Note** that, if mother develops chickenpox within 5 days before to 2 days after delivery, give the neonate ZIG. If baby develops chickenpox treat with intravenous aciclovir. **Note** that the incubation period in children who have received ZIG is extended to 28 days

## Herpes zoster

Increased incidence if immunosuppressed.

- **Clinical presentation:**
  - Prodrome of pain and tenderness in affected dermatome with fever and malaise; within a few days the same rash as varicella appears in distribution of one (sometimes two or three) unilateral dermatomes
  - If infection of cranial nerve V occurs, it may affect the cornea (ophthalmic branch)
  - If nerve VII is involved, may develop paralysis of facial nerve and vesicles in external ear (Ramsay Hunt syndrome)
- **Complications:** dissemination in immunocompromised; post-herpetic pain rare in children
- **Treatment:** supportive; intravenous aciclovir if severe and patient is immunocompromised

**Note** that VZV vaccine now available routinely in the USA, and for at-risk patients in the UK.

## 7.7 Parvovirus B19 (erythema infectiosum, 'slapped cheek' or fifth disease)

This virus affects red cell precursors and reticulocytes in the bone marrow.

- **Incubation:** approximately 1 week
- **Transmission:** respiratory secretions, blood; not infectious once rash has appeared
- **Clinical presentation:**
  - Very erythematous cheeks, then erythematous macular papular rash on trunk and extremities, which fades with central clearing giving the characteristic lacy or reticular appearance
  - Rash lasts 2–30 days
- **Complications:**
  - Aplastic crisis in chronic haemolytic diseases, e.g. sickle cell disease, thalassaemia
  - Aplastic anaemia
  - Arthritis, myalgia more common in older children/adults
  - Congenital infection with anaemia and hydrops (see Section 11)
- **Diagnosis:** clinical, serology, PCR
- **Treatment:** supportive

## 7.8 Roseola infantum (exanthem subitum or HHV-6)

- **Transmission:** respiratory secretions
- **Clinical presentation:** characteristic – sudden onset of high fever (up to 41°C) with absence of clinical localizing signs; at days 3–4 fever abruptly stops and macular/papular rash appears which lasts from <24 h to a few days:
  - This is one of the most common causes of febrile convulsions in the 6- to 18-month age group. Febrile convulsions typically occur on the first day of illness
  - This virus is ubiquitous in the population and can occur either subclinically or as a non-specific febrile illness without focus
- **Diagnosis:** Diagnostic tests are not well established. PCR is available on a research basis and serological tests are available but differentiating primary disease from reactivation is problematic
- **Treatment:** antipyretics

## 7.9 Measles

- **Incubation:** 7–14 days
- **Transmission:** respiratory droplets; infectious from 7 days after exposure, i.e. from pre-rash to 5 days after rash starts
- **Clinical presentation:**
  - Prodrôme: 3–5 days, low fever, brassy cough, coryza, conjunctivitis, Koplik spots (pathognomonic white spots opposite lower molars)
  - Eruptive stage: abrupt rise in temperature to 40°C associated with macular rash which starts behind ears and along hairline, becomes maculopapular and spreads sequentially to face, upper arms, chest, abdomen, back, legs; lasts approximately 4 days
- **Complications:**



- Otitis media, laryngitis, bronchitis
- Interstitial pneumonitis, secondary bacterial bronchopneumonia, myocarditis
- Encephalomyelitis: mainly post-infectious, demyelinating (1:1000 cases)
- Subacute sclerosing panencephalitis (see Chapter 19)
- Temporary immunosuppression for up to 6 weeks post-infection, causing increased susceptibility to secondary bacterial infections
- **Diagnosis:** clinical, viral culture, immunofluorescence, serology
- **Treatment:** symptomatic; human pooled immunoglobulin <5 days of exposure to high-risk patients only. Vitamin A in children who are malnourished or who have severe measles. Ribavirin has been used in immunocompromised children, but no controlled studies demonstrating efficacy have been performed
- **Prophylaxis:** immunization – measles, mumps, rubella (MMR)

## 7.10 Mumps

- **Incubation:** 14–21 days
- **Transmission:** respiratory droplets, infectious 24 h before to 3 days after parotid swelling
- **Clinical presentation:** mild prodrome of fever, anorexia, headache; painful bilateral (may be unilateral) salivary ± submandibular gland swelling
- **Complications:** occur as a result of viraemia early in the infection:
  - Meningoencephalitis clinically 10% (subclinically 65%):
    - Infectious – symptoms same time as parotitis
    - Post-infectious – symptoms approximately 10 days post-parotitis
  - Orchitis/epididymitis:
    - Rare in childhood, 14–35% in adolescents/adults
    - Occurs within 8 days of parotitis, abrupt onset of fever and tender, swollen testes
    - Approximately 30–40% of affected testes atrophy; may cause subfertility
  - Pancreatitis, nephritis, myocarditis, arthritis, deafness, thyroiditis
- **Diagnosis:** viral culture, serology
- **Treatment:** supportive
- **Prophylaxis:** immunization (MMR) to ensure ‘herd immunity’

## 7.11 RUBELLA (GERMAN MEASLES)

- **Incubation:** 14–21 days
- **Transmission:** respiratory droplets; transplacental
- **Clinical presentation:**
  - Mild coryza, palatal petechiae
  - Characteristic tender, retroauricular, posterior cervical and suboccipital adenopathy 24 h before rash appears, lasting 1 week
  - Rash is an erythematous maculopapular generalized rash which begins on face, spreading quickly to trunk

- **Complications:** arthritis, encephalitis, congenital rubella syndrome (see Section 11)
- **Diagnosis:** clinical, serology
- **Treatment:** supportive
- **Prophylaxis:** although a mild illness, immunization of all children prevents childbearing women contracting rubella

## 7.12 Adenovirus

- **Transmission:** respiratory droplets, contact, fomites, very contagious, strict infection control policy
- **Incubation:** 2–14 days
- **Clinical presentation:**
  - Upper respiratory tract infection
  - Conjunctivitis  $\pm$  pharyngitis
  - Gastroenteritis – more common in those aged  $<4$  years
- **Complications:** severe pneumonia (more common in infants); disseminated disease in immunocompromised patients
- **Diagnosis:** viral culture, PCR
- **Treatment:** supportive; ribavirin has been used with limited success in immunocompromised patients. Cidofovir is also used, and can be used in combination with adenovirus for severely immunocompromised children. Success is limited, and side effects, particularly renal toxicity, can be significant.

## 7.13 Enteroviruses

These include polioviruses: types 1–3; Coxsackieviruses: A and B and echoviruses.

- **Transmission:** faecal/oral and respiratory droplets, infections peak during summer and early autumn
- **Clinical presentation:**
  - Non-specific febrile illness: abrupt onset of fever and malaise  $\pm$  headache and myalgia, lasts 3–4 days
  - Respiratory manifestations: pharyngitis, tonsillitis, nasopharyngitis, lasts 3–6 days
  - GI manifestations: diarrhoea, vomiting, abdominal pain
  - Skin manifestations: ‘hand, foot and mouth’ – usually Coxsackievirus A16 and enterovirus 71; intraoral ulcerative lesions, vesicular lesions on hands and feet 3–7 mm; rash clears within 1 week
  - Pericarditis and myocarditis: usually Coxsackie B viruses
  - Neurological manifestations: aseptic meningitis (especially Coxsackievirus B5), encephalitis (especially echovirus 9), cerebellar ataxia and Guillain–Barré, syndrome
  - Although some clinical entities are more closely associated with specific enterovirus species, any of the enteroviruses can cause any of the clinical syndromes
- **Diagnosis:** viral culture, PCR. There is no place for the use of serology in the diagnosis of enteroviral infections

- **Treatment:** supportive
- **Prophylaxis:** nil for Coxsackie- and echoviruses. Polio vaccine for prevention of polio. The WHO are aiming for worldwide eradication

## 7.14 Molluscum

- **Incubation:** 2–8 weeks
- **Transmission:** direct contact with infected person or fomites or autoinoculation
- **Clinical presentation:** discrete, pearly papules 1–5 mm, face, neck, axillae and thighs
- **Diagnosis:** clinical, microscopy
- **Treatment:**
  - Self-limiting but may last months to years
  - Need to treat in immunodeficient patients or it will become widespread, e.g. remove with liquid nitrogen

## 8. PARASITIC INFECTIONS

### 8.1 Toxoplasmosis

- Caused by *Toxoplasma gondii*
- Worldwide distribution and infects most warm-blooded animals
- Cat is the definitive host and excretes oocysts in stools
- Intermediate hosts include sheep, pigs and cattle who have viable cysts in their tissues
- Human infection is by eating undercooked meat containing cysts or by ingestion of oocysts from soil; may also be acquired from blood transfusion or bone marrow transplantation
- Congenital infection (see Section 11)

### Clinical manifestations

- Often asymptomatic, or non-specific fever, malaise, myalgia, sore throat
- May also have lymphadenopathy or mononucleosis-like illness
- Complications rarely include myocarditis, pericarditis and pneumonitis, encephalitis
- Isolated ocular toxoplasmosis is usually a result of reactivation of congenital infection, but may be acquired
- Immunodeficient patients may have more serious/disseminated disease

### Diagnosis

- By serology (PCR in special cases)
- Isolation of *T. gondii* is difficult and is not performed routinely.
- Atypical lymphocytosis, eosinophilia and inversion of CD4:CD8 ratio

## Treatment

- Supportive if mild
- Pyrimethamine (and folinic acid) and sulfadiazine if symptomatic. If sulfadiazine is not tolerated, clindamycin can be used instead. A prolonged course of treatment, up to 1 year, is usual but the optimal length of treatment is not established

## 8.2 Head lice (pediculosis capitis)

- Caused by lice – *Pediculus humanus capitis*
- Itching is the most common complaint
- Adult lice or eggs (nits) may be seen in the hair
- Very common in school-aged children

## Transmission

- Occurs by direct contact with hair of infested individuals

## Diagnosis

- Clinical; can confirm by microscopy

## Treatment

- Two applications, 1 week apart, of a parasiticide lotion, left on overnight, e.g. permethrin and malathion. Resistance is developing, so if the treatment fails try another insecticide for the next course. Many people use mechanical means of louse control, e.g. ‘nit comb’. **Remember** to treat the whole family ( $\pm$  school class) at the same time.

## Malaria

See Section 9.1.

## Leishmaniasis

See Section 9.9.

## Schistosomiasis

See Section 9.10.

## Pneumocystis

## 9. TROPICAL AND GEOGRAPHICALLY CIRCUMSCRIBED INFECTIONS

Travel is increasing, with people travelling to ever more exotic regions of the world, and a mobile population brings immigrants to our shores. This presents a challenge when confronted with unusual patterns of illness. There are a number of infections that are endemic to very specific regions of the world, and others that are endemic to large swathes of the globe.

Always obtain a travel history because imported infections in returning travellers, those from abroad holidaying in the UK and recent immigrants are part of the differential diagnosis of fever.

In the last decade, 100 people of all ages have died in the UK from malaria contracted in malarious areas. Only one of these people was taking full doses of what would currently be considered an adequate antimalarial. Of these 100 cases, 94 were contracted in Africa and 6 in the countries of south Asia. Four African countries accounted for 67% of all the fatal cases (Kenya 25%, Nigeria 17%, the Gambia 14% and Ghana 11%).

However, it is not just in the developing world and the tropics that diseases unknown in the UK occur. There are a number of diseases, endemic to the Americas, that need to be considered in travellers returning from those regions. Babesiosis and Lyme disease are found on the east coast of the USA, Rocky Mountain Spotted Fever (a rickettsial infection) and ehrlichiosis occur in the south and south-west of the country, as does coccidioidomycosis, a fungal respiratory infection. Outbreaks of Hantavirus infections have occurred in Texas and Arizona and also in eastern Europe, where tularaemia can also be found. Leishmaniasis occurs in the Mediterranean as well as in Africa, and should be considered in patients returning from European holidays with symptoms. The list continues. However, a good travel and contact history can point to the possibility of an imported infection in a timely fashion, even if the precise nature of the infection is initially elusive.

### 9.1 Malaria

- Caused by *Plasmodium* spp. (*P. vivax*, *P. malariae*, *P. ovale* and *P. falciparum*) invading erythrocytes
- Endemic in the tropical world, especially sub-Saharan Africa and parts of south-east Asia
- Transmitted by bite of the female anopheles mosquito
- Congenital infection and blood transfusion-acquired infection may also occur
- *P. vivax* and *P. ovale* have hepatic stages and may cause relapses of infection
- Recrudescence of *P. falciparum* and *P. malariae* occurs from persistent low levels of parasitaemia
- *P. falciparum* malaria is the most severe and potentially fatal disease. This is the predominant species in Africa

### Clinical manifestations

Symptoms appear 8–15 days after infection, with high fevers, chills, rigors and sweats, which classically occur in a cyclical pattern depending on the type of *Plasmodium* sp. involved. Patients can present with malaria up to 3 months after returning from an endemic area and a high index of suspicion is the key to making the diagnosis:

- Headaches, abdominal pain, arthralgia, diarrhoea and vomiting are common
- Pallor and jaundice occur secondary to haemolysis
- Hepatosplenomegaly is more common in chronic infections
- Nephrotic syndrome may occur with *P. malariae*, because of immune complex deposition in the kidney
- *P. falciparum* may present as a febrile or flu-like illness with no localizing signs, or as one of the following clinical syndromes:
  - Cerebral malaria – with confusion, fits, decreased level of consciousness, coma
  - Severe anaemia with signs of haemolysis
  - Hypoglycaemia from disease (metabolic requirements of parasites) and also quinine treatment
  - Pulmonary oedema (rare in children)
  - Renal failure with acute tubular necrosis, or ‘blackwater fever’, caused by haemoglobinuria resulting from severe, acute intravascular haemolysis (rare in children)

## Diagnosis

- Thick blood films allow the detection of parasites; thin films allow species identification and determination of parasitaemia (percentage of erythrocytes harbouring parasites)
- Need at least three negative films at 12- to 24-h intervals to be confident of negative result if there is a high index of clinical suspicion
- New tests being evaluated include PCR and malarial ribosomal RNA (urine dipstix are in use in the developing world)
- **Note** that in hyperendemic areas, low-level parasitaemia, indicating a semi-immune state in children aged >4 years, is common and malaria is not necessarily the cause of the symptoms. However, people who move from these endemic areas do not retain their semi-immune status and any parasitaemia does become significant

## Treatment

- Look for and treat hypoglycaemia

Chemotherapy is based on the infecting species, possible drug resistance and disease severity.

### *P. falciparum* malaria

- In the UK, we assume that all cases of *P. falciparum* malaria are chloroquine resistant and treat with quinine, orally if possible, or intravenously if severely unwell for 3–7 days (monitor glucose and ECG if intravenous regimen used). Clindamycin should be given to children who are severely ill and/or have higher parasite counts because this increases the rate of parasite clearance.
- One dose of pyrimethamine–sulfadoxine (Fansidar) is given on the last day of quinine therapy or,

increasingly, a 3-day course of atovaquone/proguanil (Malarone) because Fansidar resistance is on the increase in Africa. Artesunate is now being recommended as first-line therapy for severe malaria in the UK

- Exchange transfusion may be warranted if parasitaemia exceeds 10%
- Monitor sequential blood smears until negative

### ***P. malariae* malaria**

- Treat with chloroquine (if no resistance)

### ***P. vivax* and *P. ovale* malaria**

- Treat with chloroquine then primaquine to eradicate the liver stage and prevent relapses. Quinine can also be used, and is increasingly the drug of choice, because chloroquine resistance is increasing on the Indian subcontinent. Check that the patient is not glucose-6-phosphate dehydrogenase (G6PD) deficient before giving primaquine

## **Prophylaxis**

- From dusk to dawn (because *Anopheles* spp. are night-biters) use protective clothing, mosquito repellents and bed nets impregnated with insecticide
- Prescribe chemoprophylaxis from 1 week before departure until 4 weeks after return:
  - Chloroquine-sensitive area – chloroquine once a week **or** proguanil daily
  - Chloroquine-resistant areas – mefloquine once a week **or** Malarone or doxycycline (in children >8 years) daily

## **9.2 Enteric (typhoid/paratyphoid) fever**

- Caused by *Salmonella typhi*, *S. paratyphi* – Gram-negative bacilli in family *Enterobacteriaceae*
- *S. typhi* found only in humans, transmitted by faecal–oral route
- Onset of illness is gradual with fever, headache, malaise, constipation (initially), diarrhoea (second week), abdominal pain, hepato-/splenomegaly, rose spots. Infants may present with Gram-negative septicaemia. Within a week, fever becomes unremitting, and delirium and disorientation may occur. The paradoxical relationship between high fever and low pulse rate is uncommon in children

## **Complications**

- Intestinal perforation occurs in 0.5–3%, severe haemorrhage in 1–10% of children
- Focal infections, e.g. meningitis, osteomyelitis, endocarditis, pyelonephritis, more common in the immunocompromised host
- Osteomyelitis and septic arthritis in children with haemoglobinopathies
- Chronic carriage – local multiplication in the wall of the gallbladder produces large numbers of salmonellae, which are then discharged into the intestine and may cause chronic carriage and

shedding (in 5% of adults but much less in children)

## Diagnosis

- Perform bacterial cultures on blood, stool, bone marrow or rose spot aspirate
- Microscopy of stool reveals many leukocytes, mainly mononuclear
- Blood leukocyte count is at the low end of normal. Frank neutropenia can occur

## Treatment

Drug choice and route of administration depend on susceptibility of organism, host response and site of infection, including:

- Ampicillin, ceftriaxone, cefotaxime, chloramphenicol; in view of resistance, a fluoroquinolone is now frequently used as first-line therapy for 14 days, although resistance to this class is developing as well
- For osteomyelitis – as above for 4–6 weeks
- For meningitis – ceftriaxone or cefotaxime for 4 weeks
- To eradicate carriage – high-dose ampicillin or amoxicillin or cholecystectomy

## Prophylaxis

- Personal hygiene and proper sanitation for food processing and sewage disposal
- Vaccine is available, but only 17–66% effective depending on type

## 9.3 Dengue fever

- Caused by an arbovirus (i.e. arthropod borne); 570 arboviruses have been identified with more than 30 human pathogens
- Dengue fever is caused by the genus *Flavivirus* (which also causes Japanese encephalitis and yellow fever)
- Transmitted by the mosquito *Aedes aegypti* – a day-biting mosquito
- Dengue fever is now endemic in south-east Asia, Central and South America, and the Caribbean

## Clinical manifestations

- Include fever for 1–7 days, frontal or retro-orbital headaches, back pain, myalgia and arthralgia (‘breakbone’ fever), nausea and vomiting
- 1–2 days after defervescence a generalized morbilliform rash occurs lasting 1–5 days. As this rash fades the fluctuating temperature reappears, producing the biphasic temperature curve

## Complications



- Dengue haemorrhagic fever (DHF) – fever, haemorrhage, including epistaxis and bleeding of the gums, and capillary fragility and fluid leakage. Complications include hepatitis, pneumonia, encephalopathy and cardiomyopathy. DHF occurs with the second infection with the arbovirus and there is an immunological component that causes augmentation of the disease and increased severity of clinical presentation. Rare in childhood

## Diagnosis

- PCR, serology, isolation of virus (**note** prior yellow fever immunization will give positive dengue IgG)

## Treatment

- None is specific; supportive only. Aggressive fluid resuscitation in DHF markedly decreases mortality

## 9.4 Viral haemorrhagic fevers

- Many different viruses are found in different parts of world, so an accurate travel history is necessary
- These diseases range from mild infections to severe acute febrile illnesses with cardiovascular collapse. Fever, headaches, myalgia, conjunctival suffusion and abdominal pain are early symptoms. Mucosal bleeding occurs with vascular damage and thrombocytopenia, and may cause life-threatening haemorrhage. Shock develops 7–10 days after the onset of illness
- Elevated alanine aminotransferase (ALT) is a poor prognostic factor in Lassa fever. Transmission is by inhalation or by contact of broken skin with the urine or saliva of infected rodents

## Diagnosis

- Serology

## Treatment

- Intravenous ribavirin for Lassa fever, especially in the first week of illness, reduces mortality
- Symptomatic management and supportive treatment for all other viral haemorrhagic fevers

## Prevention

- Strict isolation of patient and contacts. **These infections are highly contagious**
- For suspected cases – examine a malarial film only (labelled ‘Very high risk’ for laboratory staff awareness). If negative, i.e. diagnosis is NOT malaria, then contact local microbiologist/public health laboratory service urgently for transfer of the patient to the designated unit

## 9.5 Hantaviruses

- These are bunyaviruses and cause two different clinical syndromes. Rodents are the definitive hosts and are asymptomatic carriers that shed virus in their saliva and excreta. Disease is contracted through contact with infected rodents and their excreta
- Old World hantaviruses cause **haemorrhagic fever with renal syndrome**. Found throughout Asia and eastern and western Europe. Cause up to 100 000 cases a year
- New World hantaviruses, which occur in the south-west states of the USA and in the Andes region of South America, cause **hantavirus pulmonary syndrome**
- Both have an incubation period of 1–6 weeks and present with a prodrome of a non-specific flu-like illness

### Clinical presentation

#### Haemorrhagic fever with renal syndrome (Old World)

- Prodrome characterized by vascular instability, followed by renal failure presenting with oliguria, followed by polyuria, hypotension, bleeding and shock
- The European disease is milder and presents most commonly as non-specific flu-like symptoms and proteinuria. Acute severe renal failure is rare

#### Pulmonary syndrome (New World)

- Non-specific flu-like prodrome followed by the abrupt onset of progressive pulmonary oedema, hypoxaemia and hypotension. This is the result of diffuse pulmonary leakage and is most likely to be immune mediated
- After 2–4 days, there is onset of diuresis with rapid improvement and resolution of pulmonary disease

### Diagnosis

- Serology
- Characteristic full blood count abnormalities in pulmonary syndrome which include: haemoconcentration, thrombocytopenia and neutrophilia with the presence of immunoblasts on blood film

### Treatment

- Supportive and symptomatic as required. Intubation and ventilation in pulmonary syndrome. Dialysis is rarely required in haemorrhagic fever. Meticulous fluid management
- Ribavirin has been used and thought anecdotally to be useful, but evidence for efficacy is lacking

## 9.6 *Giardia*

- Caused by *Giardia lamblia*, a protozoan that produces infectious cysts
- Faecal–oral transmission
- Infection limited to small intestine and/or biliary tract
- Worldwide distribution, some animals and humans infected, may infect water supply

### Clinical manifestations

- Very varied
- Acute watery diarrhoea with abdominal pain, or foul-smelling stools and flatulence with abdominal distension and anorexia

### Diagnosis

- Stool microscopy, rarely by duodenal biopsy

### Treatment

- Metronidazole or tinidazole

## 9.7 *Amoebiasis*

- Caused by *Entamoeba histolytica*, a protozoan, excreted as cysts or trophozoites in stool of infected patients
- Faecal–oral transmission of cysts
- Worldwide distribution, with infection rates as high as 20–50% in the tropics

### Clinical manifestations

- Intestinal disease – asymptomatic or mild symptoms, e.g. abdominal distension, flatulence, constipation, loose stools
- Acute amoebic colitis (dysentery) – abdominal cramps, tenesmus, diarrhoea with blood and mucus – complications include toxic megacolon, fulminant colitis, ulceration and, rarely, perforation

### Extraintestinal disease

- Liver abscess – acute fever, abdominal pain and liver tenderness, or subacute with weight loss and vague abdominal symptoms; rupture of the abscess into the abdomen or chest may occur
- Rarely, abscesses in the lung, pericardium, brain and genitourinary tract

### Diagnosis

- Microscopy of stool, biopsy specimens and aspirates, serology if extraintestinal disease

## Treatment

- To eliminate the tissue-invading trophozoites as well as cysts
- Metronidazole followed by a luminal amoebicide, e.g. paromomycin

## 9.8 Hookworm

- Caused by *Ancylostoma duodenale* and *Necator americanus*
- Prominent in rural, tropical areas where soil may be contaminated with human faeces
- Humans are the major reservoir
- Infection is by infectious larvae penetrating the skin, usually the soles of feet

## Clinical manifestations

- May be asymptomatic
- May develop pruritus and papulovesicular rash for 1–2 weeks after initial infection
- Pneumonitis associated with migrating larvae in this phase is uncommon and usually mild

## Diagnosis

- Stool microscopy

## Treatment

- Anthelmintic drug, e.g. mebendazole (**note** also treat any associated iron-deficiency anaemia)

## 9.9 Leishmaniasis

- *Leishmania* spp. are obligate intracellular parasites of monocytes/macrophages
- Variety of hosts including canines and rodents
- Vector is the sandfly
- Incubation period is usually days to months, but may even be years
- Three major clinical syndromes:
  - Cutaneous leishmaniasis – shallow ulcer at site of sandfly bite; lesions commonly on exposed skin, i.e. face and extremities; may have satellite lesions and regional lymphadenopathy
  - Mucosal leishmaniasis – initial cutaneous infection disseminates to midline facial structures, e.g. oral and nasopharyngeal mucosa
  - Visceral leishmaniasis (kala-azar) – parasites spread throughout the reticular endothelial system and are concentrated in the liver, spleen and bone marrow. Presents with fevers, weight loss,

splenomegaly (may be massive), hepatomegaly, lymphadenopathy, anaemia, leukopenia, thrombocytopenia and hypergammaglobulinaemia

## Diagnosis

- Microscopic identification of intracellular leishmanial organisms from skin or splenic biopsy, or bone marrow
- Serology may be helpful

## Treatment

- Sodium stibogluconate or amphotericin B. Liposomal amphotericin is particularly effective and is the treatment of choice in the developed world

## 9.10 Schistosomiasis

- Caused by the trematodes (flukes) *Schistosoma mansoni*, *S. japonicum*, *S. haematobium* and others
- Humans are the principal host; snails are intermediate host
- Eggs are excreted in urine or stool into fresh water, hatch and infect snails; after further development, cercariae emerge and penetrate human skin

## Clinical manifestations

- Usually infection is asymptomatic
- May have initial transient pruritic, papular rash
- May have acute infection – Katayama fever: 4–8 weeks after infection an acute illness with fever, malaise, cough, rash, abdominal pain, diarrhoea, arthralgia, lymphadenopathy and eosinophilia
- Chronic infection with *S. mansoni* and *S. japonicum* may cause diarrhoea, tender hepatomegaly, chronic fibrosis, hepatosplenomegaly and portal hypertension
- Chronic infection with *S. haematobium* may cause dysuria, terminal microscopic haematuria, gross haematuria, frequency and obstructive uropathy
- Haematogenous spread to the lungs, liver and CNS may occur

## Diagnosis

- Identification of the eggs in stool/urine, respectively
- Bladder biopsy
- Serology

## Treatment

- Praziquantel

## 9.11 Travellers' diarrhoea

- Travellers' diarrhoea is a syndrome characterized by a twofold or greater increase in the frequency of unformed bowel movements
- Food- and water-borne diseases are the number one cause of illness in travellers
- Travellers' diarrhoea can be caused by viruses, bacteria or parasites, which can contaminate food or water
- The most important determinant of risk is the destination of the traveller
- Attack rates of 20–50% are commonly reported

### Clinical manifestations

- Diarrhoea, abdominal cramps, nausea, bloating, urgency and malaise; sometimes vomiting also occurs
- Nature of stool may indicate particular organism
- Travellers' diarrhoea usually lasts from 3 days to 7 days, but is rarely life threatening

### Enteric bacterial pathogens

- Enterotoxigenic *Escherichia coli* (ETEC) is among the most common causative agents; ETEC produces a watery diarrhoea associated with cramps and low-grade or no fever
- Salmonella gastroenteritis usually results from non-typhoidal *Salmonella* spp. that cause dysentery characterized by small-volume stools containing bloody mucus
- Shigella bacillary dysentery is seen in up to 20% of travellers to developing countries
- *Campylobacter jejuni* causes a small percentage of the reported cases of travellers' diarrhoea, some with bloody diarrhoea
- *Vibrio parahaemolyticus* is associated with the ingestion of raw or poorly cooked seafood

Less common bacterial pathogens include other diarrhoeagenic *E. coli*, *Yersinia enterocolitica*, *Vibrio cholerae* O1 and O139, non-O1 *V. cholerae*, *V. fluvialis*, and possibly *Aeromonas hydrophila* and *Plesiomonas shigelloides*.

### Viral enteric pathogens

- Rotaviruses and Norwalk-like virus may cause travellers' diarrhoea

### Parasitic enteric pathogens

- These include *Giardia intestinalis*, *Entamoeba histolytica*, *Cryptosporidium parvum* and *Cyclospora cayentanensis*. The likelihood of a parasitic aetiology is higher when diarrhoeal illness is prolonged. *Entamoeba histolytica* should be considered when the patient has dysentery or invasive diarrhoea (bloody stools)

## Treatment

- Antimotility agents should NOT be used in children. Occasionally in adolescents, similar to adults, they may be used to provide prompt symptomatic but temporary relief of uncomplicated travellers' diarrhoea. However, they should **not** be used by people with high fever or with blood in their stools
- Oral rehydration solutions and plenty of fluids should be drunk to prevent dehydration
- Antibiotics should be reserved for: those with severe diarrhoea that does not resolve within several days; if there is blood or mucus, or both, in the stools; if fever occurs with shaking chills

## Prevention

- Treatment of water:
  - Boiling for at least 5 min is the most reliable method to make water safe to drink
  - Chemical disinfection can be achieved with either iodine or chlorine, with iodine providing greater disinfection in a wider set of circumstances
- Food:
  - Any raw food can be contaminated, particularly in areas of poor sanitation
  - Foods of particular concern include salads, uncooked vegetables and fruit, unpasteurized milk and milk products, raw meat and shellfish
  - Some fish are not guaranteed to be safe even when cooked because of the presence of toxins in their flesh. Tropical reef fish, red snapper, amber jack, grouper and sea bass can occasionally be toxic at unpredictable times if they are caught on tropical reefs

## 10. NEW AND EMERGING INFECTIONS

### 10.1 Severe acute respiratory syndrome

- New infectious disease. Restricted to China, Hong Kong and Vietnam and visitors to those regions and their contacts, resulting in outbreaks in Toronto and Singapore. Probably originated in the animal populations and crossed over into humans. Disease restricted to a single outbreak
- **Aetiology:** novel coronavirus
- **Incubation period:** 2–10 days. More severe cases present earlier
- **Clinical presentation:** non-specific flu-like prodrome followed by fever, shortness of breath and diffuse pneumonia, and acute respiratory distress syndrome. Associated diarrhoea in some patients. Less severe in children and few cases <15 years; 10% mortality rate
- **Diagnosis:** PCR of nasopharyngeal aspirate, stool and urine. Serology is useful for epidemiological purposes only
- **Treatment:** No effective treatment. Ribavirin has been used and also steroids in the more severe affected patients, with limited success. Intensive care with mechanical ventilation required for a large percentage of infected patients

## 10.2 West Nile virus

- West Nile virus is a flavivirus. Widely distributed throughout Africa, the Middle East, Asia, Australia and parts of Europe. First detected in the USA in 1999 and is now widespread throughout the continent. Primary hosts are birds and the vectors are mosquitoes. Peak infection is late summer, but sporadic cases occur
- **Clinical presentation:** most patients present with a self-limiting febrile flu-like infection, characterized by headaches, myalgias, malaise, back pain and loss of appetite. Vomiting, diarrhoea, abdominal pain and pharyngitis are common, and the disease lasts 3–10 days
- The mortality rate in this group is approximately 2%
- Neurological complications occur in <1% of patients, and elderly and immunocompromised individuals are more at risk. This presents typically as an encephalitis with muscle weakness, and in some cases a flaccid paralysis. Parkinsonian-like features can also occur
- **Diagnosis:** serology
- **Treatment:** supportive

## 10.3 Avian influenza virus

- The H5N1 strain of avian influenza virus is endemic in the bird population in south-east Asia, with sporadic human spread, and culling of domestic birds has been necessary to prevent further spread. Pigs are an important reservoir that could facilitate mutation of the virus
- Concern that close proximity of birds, swine and humans in south-east Asia will facilitate mutation and, although no cases have been reported outside this region, there is widespread concern that mutation and spread to the human population will cause a severe influenza pandemic worldwide
- >90 cases in humans in 2004–2005. Mortality rate of 68%. Predominance in children and young adults
- **Treatment:** oseltamivir

## 10.4 H1N1 influenza virus: swine flu

The H1N1 strain of influenza emerged in Mexico during the summer of 2009 and quickly spread around the world. Most cases were mild or asymptomatic, but, in a small proportion of cases, it caused severe illness and death. This is a novel strain of influenza, sufficiently different to other circulating strains that there is no cross-over immunity from previous influenza infections or the previous season's immunization. It was thought to be similar to the strain that caused a large outbreak in the 1950s and this accounts for the relative immunity enjoyed by the over-60 age group, the group usually most severely affected by influenza. The most severely affected in this pandemic were children and young adults. In 2010 it was the predominant circulating influenza strain during the influenza season.

- **Treatment:** oseltamivir or zanamavir. Not susceptible to amantidine or ramantidine



# 11. CONGENITAL INFECTIONS

Congenital infections are acquired *in utero*, usually transplacentally, during maternal infection. Manifestations are most severe if acquired in the first trimester.

Suspect if:

- Small for gestational age
- Microcephaly or hydrocephalus
- Ocular defects
- Hepatosplenomegaly
- Thrombocytopenia
- Developmental delay/fits

## 11.1 Diseases

### CMV, congenital rubella syndrome, toxoplasmosis

- Approximately two-thirds of pregnancies complicated by rubella during the first 8 weeks of gestation will result in fetal death or severe abnormality
- There is a 40% risk of toxoplasmosis transmission from mother to fetus
- In CMV and toxoplasmosis, approximately 10% of infected infants are clinically affected at birth, although symptoms will often become apparent during childhood

### Characteristic features of CMV, rubella and toxoplasmosis infection

Abnormality	Rubella	CMV	Toxoplasmosis
<i>Neurological:</i>			
Sensorineural hearing loss	+++	++	+
Microcephaly	+	++	+
Hydrocephalus	-	-	++
Calcification	-	++ (peri-ventricular)	++ (widespread)
<i>Eyes:</i>			
Micro-ophthalmia	+	-	+
Cataracts	+++	-	+
Chorioretinitis	+	++	+++
Growth retardation	++	+++	+
Hepatosplenomegaly	+++	+++	++
Petechiae ('blueberry muffin' rash)	++	++	+
Cardiac malformations	++	-	-
Pneumonitis	+	++	+
Bony involvement	++	-	

## Parvovirus B19

- Women who become infected with parvovirus B19 during the first 20 weeks of pregnancy have a 9% fetal loss
- Hydrops fetalis occurs in approximately 3% if the mother is infected between 9 and 20 weeks' gestation

## **Congenital varicella**

- Infection during the first or second trimester may rarely cause congenital varicella syndrome (0.5–2%)
- Skin scarring, limb malformation/shortening, cataracts, chorioretinitis, micro-ophthalmia, microcephaly, hydrocephalus

## **Herpes simplex virus**

- Vast majority of infants are infected peripartum, only 5% transplacentally
- Cutaneous scars or vesicles
- Chorioretinitis, keratoconjunctivitis, micro-ophthalmia
- Microcephaly, intracranial calcifications
- Hepatosplenomegaly
- Developmental delay

## **Syphilis**

- High transmission rate, 40% mortality rate if left untreated
- 'Snuffles', congenital nephrotic syndrome, chorioretinitis, glaucoma
- Osteochondritis, periostitis
- Hepatosplenomegaly, lymphadenopathy
- Rash – maculopapular, desquamative, bullous, condylomas

## ***Mycobacterium tuberculosis***

- Very rare, high mortality
- Presents as disseminated disease with fevers and often respiratory distress
- Needs Mantoux testing, chest radiograph, lumbar puncture, quadruple therapy + steroids if meningitis is confirmed

## **Diagnosis**

- 'TORCH screen' – toxoplasmosis, 'other', rubella, CMV and herpes-specific IgM in neonates <4 weeks old implies congenital infection
- Screen for specific infection based on clinical findings in neonate and mother, rather than requesting a TORCH screen
- **Note:** look at specific antibody responses in mother's booking-visit blood samples and post-delivery blood samples to see rise/fall in titres depending on time of infection acquisition

- PCR can be useful in some infections
- Ophthalmological examination – characteristic retinal changes

## Treatment

- Prevention through immunization is the only way to reduce the risk of congenital rubella
- Spiramycin may be used for toxoplasmosis in pregnancy to reduce transmission to the fetus.  
Affected infants are treated with pyrimethamine and sulfadiazine after birth
- Ganciclovir or valganciclovir may be used in cases of congenital CMV. At present 6 weeks of treatment soon after birth is recommended to reduce hearing loss. There are ongoing studies to assess the efficacy of longer courses of therapy and therapy later in childhood
- Aciclovir is recommended for up to a year in patients with neonatal herpes simplex
- Penicillin is used to treat syphilis
- HAART used for HIV infection
- Anti-TB treatment

## 12. MISCELLANEOUS

### 12.1 Differential diagnosis of prolonged fever

Systemic bacterial disease:	Viral disease:
Salmonellosis	CMV
Mycobacterial infection	Hepatitis viruses
Brucellosis	EBV
Leptospirosis	Human herpesvirus-6
Spirochaete infections	

Focal bacterial infections:	Parasitic infections:	Other infections
Abscesses	Malaria	Chlamydia
Sinusitis	Toxoplasmosis	Rickettsia
Osteomyelitis	Leishmaniasis	Fungi
Endocarditis		
Urinary sepsis		

### Non-infectious diseases:

Collagen vascular diseases: systemic lupus erythematosus (SLE), juvenile inflammatory arthritis (JIA)

Familial Mediterranean fever

Kawasaki disease

Sarcoidosis

Inflammatory bowel disease

Malignancies  
Drugs  
Haemophagocytic lymphohistiocytosis  
Autonomic/CNS abnormalities

---

## 12.2 Differential diagnosis of cervical lymphadenopathy

### Differential diagnosis of cervical lymphadenopathy

Cervical abscess	Malignancy
Tuberculosis (usually atypical)	Infectious mononucleosis
Cat-scratch fever (caused by <i>Bartonella henselae</i> )	Toxoplasmosis
Gram-negative organism	Brucellosis
Mumps	Salivary stones

## 12.3 Infections commonly associated with atypical lymphocytosis

- EBV
- CMV
- Toxoplasmosis
- Mumps
- Tuberculosis
- Malaria

## 12.4 Diseases associated with eosinophilia

An increase above  $0.4 \times 10^9/l$  is seen with:

- Allergic disease, e.g. asthma, eczema
- Parasitic disease, e.g. hookworm, amoebiasis, ascariasis, tapeworm infestation, filariasis, schistosomiasis
- Recovery from acute infection
- Skin disease, e.g. psoriasis, pemphigus
- Hodgkin disease
- Polyarteritis nodosa
- Drug sensitivity
- Hypereosinophilia syndrome
- Eosinophilic leukaemia (very rare)

## 12.5 Causes of hydrops fetalis

- 10–15% ‘immune’ aetiology:
  - Fetal anaemia caused by anti-D, anti-Kell and anti-C antibodies
- 85–90% non-immune cause:
  - Human parvovirus B19 infection (most common), CMV, toxoplasmosis, syphilis, leptospirosis
  - Aneuploidy
  - Cardiac cause, e.g. supraventricular tachycardia and congenital complete heart block
  - Primary hydrothorax
  - Cystic hygroma
  - Twin–twin transfusion syndrome
  - Massive transplacental haemorrhage
  - Fetal akinesia and muscular dystrophy

## 12.6 Oxazolidinones: a new class of antibiotics

### Linezolid

- Active against meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci:
  - Bacteriostatic agent
  - Good CNS penetration
- Does not have good activity against Gram-negative organisms
- Reserve for those with infections resistant to other antibacterial agents
- Side effects include myelosuppression – monitor blood count weekly

## 12.7 Echinocandins: a new class of antifungals

- Active against *Aspergillus* and *Candida* spp. Fungistatic in aspergillosis, but fungicidal in candidal disease. Useful as adjunctive therapy together with either amphotericin B (AmBisome) or voriconazole in severe fungal infections
- Widely distributed in all tissues and has good CNS penetration when disease is present
- Intravenous preparation only
- Adverse effects: raised aminotransferases, headaches and gastrointestinal disturbances

## 12.8 Erythema multiforme

- Characteristic target lesions; also macules, papules, weals, vesicles and bullae
- Systemic symptoms common – fever, malaise, arthralgia
- Stevens–Johnson syndrome – severe erythema multiforme with mucosal bullae in mouth, anogenital region and conjunctiva

## Causes

- Idiopathic (> 50%)
- Herpes simplex
- *Mycoplasma* spp.
- Viruses – enteroviruses
- Drugs – sulfonamides, penicillins, barbiturates

## Treatment

- Treat underlying cause; supportive; steroids in severe erythema multiforme (early)

## 12.9 Erythema nodosum

Inflammatory disease of skin and subcutaneous tissues characterized by tender, red nodules predominantly pretibial (also arms and other areas):

- Streptococcal upper respiratory tract infection
- Sarcoid
- Primary tuberculosis
- Ulcerative colitis
- Drugs (sulfonamides, contraceptive pills, bromides)
- Other – leprosy, histoplasmosis, psittacosis, lymphogranuloma venereum, coccidioidomycosis

## Treatment

- Antimicrobials specific to the infection
- Steroids: systemic most effective

## 12.10 Anthrax

- Caused by the Gram-positive organism *Bacillus anthracis*
- Wild and domestic animals in Asia, Africa and parts of Europe carry the bacterium
- The bacterium can exist as a spore, which allows it to survive in the environment (e.g. in the soil)

### Cutaneous anthrax (95% of cases)

- Caught by direct contact with the skin or tissues of infected animals. A lesion appears on the skin, often on the head, forearms or hands, and develops into a characteristic ulcer with a necrotic centre. It is rarely painful. Untreated, the infection can spread to cause bacteraemia, which can be fatal in 5–20% of cases

## Inhalation anthrax

- Much less common. Caused by breathing in anthrax spores. Symptoms begin with a flu-like illness, followed by respiratory difficulties and shock after 2–6 days. High fatality rate

## Intestinal anthrax

- Very rare form of food poisoning, which results in severe gut disease, fever and septicaemia. Mortality rate of up to 50%
- Vaccine – available for very-high-risk groups only
- Post-exposure prophylaxis with antibiotics can be very effective in preventing disease, provided that it is given early enough

## Treatment

- High-dose penicillin and doxycycline or ciprofloxacin

## 12.11 Botulism

- Botulism is caused by a botulinum toxin, produced by the bacterium *Clostridium botulinum*
- The bacterium is anaerobic and common in the soil in the form of spores
- Food-borne botulism occurs when the spores of *C. botulinum* have germinated and the bacteria have reproduced in an environment (usually food) outside the body and produced toxin. The toxin is consumed when the food is eaten
- The toxin is destroyed by normal cooking processes

## Clinical manifestations

Botulism is a neuromuscular disorder that can be classified into three categories:

- Food borne:
  - Onset of symptoms is usually abrupt, within 12–36 h of exposure
  - Symmetrical, descending, flaccid paralysis occurs, typically involving the bulbar musculature initially
  - Sometimes diarrhoea and vomiting occur
  - Most cases recover, but the recovery period can be many months; the disease can be fatal in 5–10% of cases
- Infant botulism:
  - Extremely rare, but occurs when spores are ingested that germinate, multiply and release toxin in the intestine; not related to food ingestion in this population; more common in breast-fed babies and in certain regions of the world
  - Incubation period is much longer: 3–30 days

- Presents with ‘floppy infant’ with poor feeding, weak cry, generalized hypotonia, constipation
- Wound botulism:
  - Same symptoms as other forms, but occurs when the organisms get into an open wound and are able to reproduce in an ‘anaerobic’ environment

## Diagnosis

- Enriched selective media are used to culture *C. botulinum* from stools and food
- A toxin neutralization assay can identify botulinum toxin in serum, stool or food
- Electromyography has characteristic appearances

## Treatment

- Supportive care, especially respiratory (e.g. ventilation) and nutritional
- Antitoxin
- Baby Big (botulism immune globulin): treatment for infant botulism – effective if given early in the disease process. Shortens course of the illness, decreases intensive care time
- Concerns about the effectiveness and side effects of the vaccine against botulism; it is not widely used
- Immunity to botulism toxin does not develop, even with severe disease

## Prevention

Education about food preparation.

## Therapeutics

Botulinum A toxin, in small doses, is used therapeutically to prevent excessive muscular activity, e.g. in torticollis, cerebral palsy and recently in cosmetics to reduce wrinkles.

## 12.12 Bovine spongiform encephalopathy and new variant Creutzfeldt–Jakob disease

- Transmissible spongiform encephalopathies (TSEs) are caused by proteinaceous infectious particles or prions. These are abnormal isoforms of a cell-surface glycoprotein designated PrP
- Disease is caused when a disease-specific isoform, PrP<sup>Sc</sup>, interacts with PrP producing conversion to PrP<sup>Sc</sup>. This protein is not readily digested by proteases and therefore accumulates, causing a rapidly progressive and fatal encephalopathy
- PrP<sup>Sc</sup> is very resistant to standard methods of sterilization and disinfection. The genotype of polymorphic codon 129 of the human PrP gene appears to influence susceptibility to infection and disease phenotype. Of white people 37% are methionine homozygous (MM), 12% are valine homozygous (VV) and 51% are heterozygous (MV). Cases of new variant Creutzfeldt–Jakob disease (nv-CJD) have been found in MM individuals



## Creutzfeldt–Jakob disease

The principal human spongiform encephalopathy. Features include a progressive dementia, movement disorder and death in a median of 4 months. The incidence is between 0.5 and 1 case per million. Most cases present between 55 and 75 years of age and most have no known cause; 15% have a hereditary predisposition to CJD, with recognized mutations of the human *PrP* gene on chromosome 20. A small number of iatrogenic cases have occurred following the use of contaminated growth hormone.

## Kuru

A disease of motor incoordination, this was endemic in Papua New Guinea in the 1950s and 1960s. Kuru was a TSE spread by the ritual cannibalism of deceased relatives. Cannibalism ceased in the late 1950s, but there are still a few cases in older adults indicating a long incubation period.

## New variant CJD

This was first reported with 10 cases in 1996. The source appeared to be bovine spongiform encephalopathy (BSE), acquired after the ingestion of infected cattle. The disease starts as a psychiatric illness followed by ataxia, myoclonus, akinetic mutism and death after about 12 months. There are now more than 100 cases. The incubation period may be very long and therefore the total number of cases is difficult to predict. Only six cases in children have been identified since 1997, the youngest being 12 at diagnosis.

## 13. FURTHER READING

American Academy of Paediatrics (2009). *Report of the Committee on Infectious Diseases. Red Book*. Elk Grove Village, IL: American Academy of Paediatrics.

BMA and RPSGB (2011). *British National Formulary for Children*, March.

Feigin R, Cherry J (2009). *Textbook of Paediatric Infectious Diseases*, 6th edn. Philadelphia, PA: WB Saunders.

Gardiner M, ed. (2009). *Training in Paediatrics*. Oxford: Oxford University Press.

Kliegman RM, ed. (2010). *Nelson Textbook of Paediatrics*, 19th edn. Philadelphia, PA: WB Saunders.

Shingadia D, Davies EG, eds (2011). *Manual of Childhood Infections. The Blue Book*. Oxford: Oxford University Press.

## WEBSITES

Centers for Disease Control (CDC): [www.cdc.gov](http://www.cdc.gov)

Health Protection Agency (HPA): [www.hpa.org.uk](http://www.hpa.org.uk)

---

# Chapter 16

## Metabolic Medicine

*Mike Champion*

---

## CONTENTS

### 1. Basic metabolism

- 1.1 Carbohydrate metabolism
- 1.2 Protein metabolism
- 1.3 Fat metabolism

### 2. Approach to the metabolic case

- 2.1 Inheritance
- 2.2 Presentation
- 2.3 Examination
- 2.4 Investigations
- 2.5 Acute management
- 2.6 Long-term management

### 3. Disorders of amino acid metabolism

- 3.1 Phenylketonuria
- 3.2 Tyrosinaemia (type 1)
- 3.3 Maple syrup urine disease
- 3.4 Homocystinuria
- 3.5 Non-ketotic hyperglycinaemia

### 4. Organic acidaemias

- 4.1 Propionic, methylmalonic and isovaleric acidaemias
- 4.2 Glutaric aciduria type 1

### 5. Urea cycle defects

## **6. Fat oxidation disorders**

[6.1 Medium-chain acyl-CoA dehydrogenase deficiency](#)

[6.2 Long-chain defects](#)

## **7. Mitochondrial disorders**

[7.1 Mitochondrial genetics](#)

[7.2 Clinical features](#)

## **8. Disorders of carbohydrate metabolism**

[8.1 Glycogen storage disease](#)

[8.2 Galactosaemia](#)

[8.3 Hereditary fructose intolerance](#)

## **9. Lipid disorders**

[9.1 Hypertriglyceridaemias](#)

[9.2 Hypercholesterolaemias](#)

[9.3 Abetalipoproteinaemia](#)

## **10. Peroxisomal disorders**

[10.1 Zellweger syndrome](#)

[10.2 X-linked adrenoleukodystrophy](#)

## **11. Mucopolysaccharidoses**

[11.1 Classification](#)

[11.2 Hurler syndrome](#)

## **12. Sphingolipidoses**

[12.1 Tay–Sachs disease](#)

[12.2 Gaucher disease](#)

[12.3 Niemann–Pick disease](#)

[12.4 Fabry disease](#)

## **13. Miscellaneous**

[13.1 Porphyria](#)

[13.2 Smith–Lemli–Opitz syndrome](#)

[13.3 Congenital disorders of glycosylation](#)

[13.4 Lesch–Nyhan syndrome](#)

[13.5 Menkes syndrome](#)

[13.6 Ketotic hypoglycaemia](#)

## **14. Screening**

[14.1 Principles of screening](#)

[14.2 UK neonatal screening programme](#)

## **15. Further reading**

---

# Metabolic Medicine

---

## 1. BASIC METABOLISM

### 1.1 Carbohydrate metabolism

Glucose has three metabolic fates in the body: oxidation for energy, storage as glycogen, and conversion to amino acids and triglycerides.

A steady supply of adenosine triphosphate (ATP) is needed to power each cell's essential processes. This ATP is usually supplied from the oxidation of glucose provided in the diet and from glycogen stores. In the fasted state, the hormone-mediated response is to draw on the body's reserves, fat and protein (catabolism), to make up the fuel shortfall to generate ATP.

The diet rarely contains glucose as the only carbohydrate source; other carbohydrates, e.g. fructose, galactose, lactose, need to be converted to glucose first before they can be used for energy.

### Glycolysis

Glycolysis takes place in the cytoplasm of all cells and describes the breakdown of one molecule of glucose to produce two molecules of pyruvate. It can occur under aerobic (large energy production via the tricarboxylic acid [TCA] cycle and oxidative phosphorylation) or under anaerobic conditions (small energy production via lactate). Glycolysis provides an emergency mechanism for energy production when oxygen is limited, i.e. in red cells (which have no mitochondria, so glycolysis is their only means of energy production) or in skeletal muscle during exercise. Glycolysis also provides intermediates for other metabolic pathways, e.g. pentoses for DNA synthesis. The three enzyme steps are irreversible.

### Pyruvate metabolism

Pyruvate, produced by glycolysis and other metabolic pathways, can be converted to oxaloacetate (by pyruvate carboxylase) for entry into the TCA cycle, or acetyl-CoA (by pyruvate dehydrogenase), which has a number of potential fates:

- Oxidation in the TCA cycle

- Fatty acid synthesis
- Ketone body synthesis
- Steroid synthesis

## Tricarboxylic acid cycle

This cycle is present in all cells with mitochondria (not red cells) and provides the final common pathway for glucose, fatty acids and amino acid oxidation via acetyl-CoA or other TCA cycle intermediates. The cycle's main function is the provision of reduced cofactors (reduced nicotinamide adenine dinucleotide or NADH, reduced flavin adenine dinucleotide or FADH<sub>2</sub>) which donate electrons to the respiratory chain for ATP production (see Section 7). The cycle also provides metabolic intermediates for other synthetic pathways, e.g. amino acid synthesis and has a key regulatory role in metabolism.

## Glycogen metabolism

Glycogen is a branched glucose polymer stored in the liver, kidney and muscle for the rapid release of glucose when needed. Liver glycogen is a store to release glucose to the rest of the body, whereas muscle glycogen supports muscle glycolysis only.

**Glycogen synthesis** is promoted by insulin and involves:

- Uridine diphosphate (UDP)-glucose synthesis (glucose donor) from glucose 1-phosphate
- Elongation of glycogen (glucose linked to existent glycogen strand ( $\alpha$ -1,4-glycosidic bond))
- Branch formation ( $\alpha$ -1,6-glycosidic bond)

Glycogenolysis is promoted by adrenaline and glucagon and involves:

- shortening of chain to release glucose 1-phosphate
- Sequential removal until the branch point is reached
- Removal of the branch point

## 1.2 Protein metabolism

Proteins are assembled from amino acids, which are composed of an amino group metabolized to urea via ammonia and a carbon skeleton which has a number of potential metabolic fates: acetyl-CoA, pyruvate and ketone bodies.

Amino acids may be used for protein synthesis or converted to other non-essential amino acids, (transamination) or oxidized via the TCA cycle. Essential amino acids cannot be synthesized in the body. There is a continual turnover of the body's protein because amino acids in the body's amino acids pool are used for protein synthesis and then broken back down to amino acids. Protein cannot be stored and therefore any amino acids not used are catabolized and hence, to remain in neutral nitrogen balance, protein is an essential constituent of a healthy diet.

**Gluconeogenesis** is the new synthesis of glucose from non-carbohydrate sources such as amino acids, lactate and glycerol. This usually occurs in the liver but also occurs in the kidney in prolonged starvation. Gluconeogenesis is promoted by glucagon, cortisol and adrenocorticotrophic hormone (ACTH).

## 1.3 Fat metabolism

Fat has the highest caloric value and therefore is an essential energy source. Triglycerides comprise three fatty acid molecules and one glycerol molecule which are broken down by lipase (**lipolysis**). The released glycerol is converted to glyceraldehyde 3-phosphate in the liver, a key intermediate of both **glycolysis** and **gluconeogenesis**. The fatty acids undergo  $\beta$ -oxidation (see Section 6) within mitochondria, which shortens the fatty acid by two carbons per cycle, releasing acetyl-CoA for entry to the TCA cycle or the production of ketone bodies.

Fatty acids can be synthesized from acetyl-CoA by adding two carbons sequentially to the elongating fatty acid chain (**lipogenesis**). This occurs mainly in the liver, adipose tissue, lactating mammary gland and, to a minor degree, the kidney. Essential fatty acids cannot be synthesized by the body because the enzyme required to form double bonds beyond nine carbons in length is not present. The principal essential fatty acids are linoleic (C18:2) and  $\alpha$ -linolenic (C18:3) acids. Walnut oil is used as a rich source in children on very-low-fat diets.

## 2. APPROACH TO THE METABOLIC CASE

### 2.1 Inheritance

Inborn errors of metabolism are individually rare but collectively they have an incidence of about 1 per 800 births. Autosomal recessive inheritance is the most common. Exceptions include the following:

- **X-linked recessive:** Lesch–Nyhan syndrome, Hunter syndrome, ornithine transcarbamylase (OTC) deficiency, Fabry disease, adrenoleukodystrophy
- **Autosomal dominant:** porphyrias (some recessive), familial hypercholesterolaemia
- **Matrilineal:** mitochondrial DNA point mutations

### 2.2 Presentation

Presentation is notoriously non-specific, so clues should be sought in the history. The most common misdiagnosis is sepsis.

### Clues from the history



- Consanguineous parents
- Previous sudden infant death (especially late, i.e. >6 months)
- Ethnicity (for certain conditions only)
- Previous multiple miscarriages (suggesting previously affected fetuses)
- Maternal illness during pregnancy, e.g.:
  - Acute fatty liver of pregnancy (AFLP) and haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: association with carrying fetus with long-chain fat oxidation defect
  - Increased fetal movements (*in utero* seizures)
- Faddy eating (avoidance of foods that provoke feeling unwell)
- Previous encephalopathic or tachypnoeic episodes (latter implies acidosis)

Inborn errors of metabolism present at times of metabolic stress, e.g.:

- Neonatal period
- Weaning (increased oral intake, new challenges, e.g. fructose)
- End of first year (slowing in growth rate, so more protein catabolized as less used for growth. May exceed metabolic capacity of defective pathway)
- Intercurrent infections
- Puberty

Neonatal presentation can be divided into four groups for diagnostic purposes.

1. Failure to make or break complex molecules
2. Intoxication
3. Energy insufficiency
4. Neonatal seizures

### **Failure to make or break complex molecules**

These are usually dysmorphic syndromes at birth because of the absence of structural molecules that are important for embryogenesis (failure to make complex molecules), e.g.

- Smith–Lemli–Opitz syndrome (cholesterol synthesis defect)
- Zellweger syndrome (peroxisomal disorder)
- Congenital disorders of glycosylation (glycosylation defects)

Many storage disorders appear normal at birth and become progressively more obvious with time as storage accumulates (failure to break down complex molecules).

### **Intoxication**

Key feature is a symptom-free period before decompensation while the toxic metabolites build up, i.e. once feeds are established and the neonate no longer relies on the placenta for clearance. Classic presentation is collapse on day 3 of life. Differential diagnosis includes sepsis and duct-dependent cardiac problems.

- Aminoacidopathies: tyrosinaemia, maple syrup urine disease (MSUD)

- Urea cycle defects (UCDs)
- Organic acidaemias (OAs)
- Sugar intolerances: galactosaemia

### **Energy insufficiency**

Absence of symptom-free period with immediate onset of symptoms in congenital lactic acidosis. There is a spectrum of severity and some may take longer to decompensate fully:

- Respiratory chain defects
- Pyruvate metabolism defects (pyruvate dehydrogenase, pyruvate carboxylase)

The group includes conditions that present only if there is a delay in fuel provision, e.g. fat oxidation defects, and glycogenolysis and gluconeogenesis defects; these may not present for some months or longer, e.g.

- Fat oxidation defects – medium-chain acyl-CoA dehydrogenase (MCAD), long-chain hydroxyacyl-CoA dehydrogenase (LCHAD), very-long-chain acyl-CoA dehydrogenase (VLCAD)
- Glycogen storage disease (GSD) types I and III
- Defects of gluconeogenesis – fructose biphosphatase deficiency

### **Neonatal seizures**

- Suspect if evidence for *in utero* seizures or early onset in the absence of birth asphyxia

### **Effective treatment**

- Pyridoxine-dependent seizures
- Pyridoxal phosphate-dependent seizures
- Biotinidase deficiency
- GLUT1 (glucose transporter type 1) deficiency
- Creatine disorders

### **No effective treatment**

- Molybdenum cofactor deficiency
- Non-ketotic hyperglycinaemia (NKH)
- Peroxisomal disorders

## **2.3 Examination**

Clinical examination may reveal few clues in many disorders of intermediary metabolism. Dysmorphic features may suggest certain diagnoses. Odours are usually unhelpful and rarely significant (exceptions include MSUD, in which the nappies smell sweet, and isovaleric acidaemia, in which there is a pungent sweaty odour). Eyes should be carefully examined for corneal clouding

(mucopolysaccharidoses, cystinosis), cataracts (galactosaemia, peroxisomal, mitochondrial), pigmentary retinopathy (fat oxidation, mitochondrial) and cherry-red spot (Tay–Sachs disease, Niemann–Pick disease, Sandhoff disease, gangliosidosis G<sub>M1</sub>). Organomegaly is a key revealing sign. Hepatosplenomegaly is a feature of storage disorders. Massive hepatomegaly in the absence of splenomegaly suggests glycogen storage disease because glycogen is not stored in the spleen. More prominent splenomegaly is suggestive of Gaucher disease.

## 2.4 Investigations

Perform investigations at the time of decompensation when diagnostic metabolites are most likely to be present and avoid the need for stress tests at a later date, e.g. diagnostic fast.

### Key initial metabolic investigations

- Blood gas (venous, capillary or arterial)
- Glucose
- Lactate
- Ammonia
- Amino acids (plasma)
- Acylcarnitines
- Organic acids (urine)
- Ketones (urinary dipstick)

### Perimortem investigations

There are occasions when a metabolic diagnosis is considered in a patient in extremis. It is essential to take the samples that will help secure the diagnosis and hence inform future reproductive choices before the opportunity is lost.

### Perimortem investigations

Blood	
Red cells	Refrigerate 4°C
Plasma	Freeze –20°C
Acylcarnitines	Four spots on a Guthrie card
DNA	EDTA sample
Urine	Freeze –20°C
Skin biopsy	If culture medium is not available, sample will survive happily in 0.9% saline in the fridge over a weekend at 4°C before being sent to the lab. Do NOT freeze

Muscle or liver biopsy is taken only if specific diagnosis is considered that requires this for confirmatory enzymology. Sample must be frozen <1 hour after death to ensure meaningful

interpretation before autolysis of the body's enzymes.

## Acid–base status

Anion gap =  $\text{Na}^+ + \text{K}^+ - (\text{Cl}^- + \text{HCO}_3^-)$

A normal anion gap (10–18 mmol/l) in the presence of metabolic acidosis signifies bicarbonate loss rather than an excess of acid, e.g. renal or gut. Although the pH may be normal, a low  $\text{PCO}_2$  (<4.5 kPa) indicates significant acid–base disturbance. Marked ketosis is unusual in the neonate and is therefore highly suggestive of an underlying metabolic disorder. Urea cycle defects may initially present with a mild respiratory alkalosis. Ammonia acts directly on the brain stem as a respiratory stimulant.

## Characteristics of metabolic and respiratory acidosis and alkalosis

---

### Metabolic acidosis (low pH, low $\text{CO}_2$ )

---

- Increased acid load
  - Organic acids
    - lactate      hypotension, hypoxia
    - mitochondrial, OAs
  - ketosis      diabetic ketoacidosis, OAs
- Drugs/poisoning
- Reduced acid excretion
  - distal renal tubular acidosis
  - renal failure

- Bicarbonate loss
  - gastrointestinal
    - severe diarrhoea
    - total villus atrophy
  - renal loss
    - proximal renal tubular acidosis

---

### Metabolic alkalosis (high pH, high $\text{CO}_2$ )

---

- Increased alkali load
  - Drugs/poisoning
- Loss of unbuffered acid
  - gastrointestinal
    - gastric aspiration
    - pyloric stenosis
    - chloride-losing diarrhoea
  - renal

mineralocorticoid excess  
(Cushing, Conn)  
diuretics  
correction of chronic raised CO<sub>2</sub>

---

OAs, organic acidaemias.

---

## **Respiratory acidosis (low pH, high CO<sub>2</sub>)**

---

Hypoventilation

encephalopathy (includes metabolic, drugs, anoxia, trauma, raised intracranial pressure, etc.)  
neural/neuromuscular  
thoracic restriction  
    dysostosis multiplex  
    kyphoscoliosis  
lung compression  
    pleural effusion  
    pneumothorax  
lung disease  
    airway obstruction  
    pneumonia etc

---

## **Respiratory alkalosis (high pH, low CO<sub>2</sub>)**

---

Hyperventilation

hyperammonaemia  
drugs, e.g. salicylate  
mechanical ventilation/overbagging pain/anxiety

---

## **Metabolic acidosis**

**Key investigations: ketones, glucose, lactate, ammonia**

### **Metabolic acidosis with ketosis**

- Diabetes
- Organic acidaemias
- Ketolysis defects,
- Mitochondrial disorders
- Gluconeogenesis defects
- Adrenal insufficiency

### **Metabolic acidosis without ketosis**

- Fat oxidation defects
- Pyruvate dehydrogenase deficiency
- Ketone synthesis defects
- Renal tubular acidosis

# Hypoglycaemia

**Hypoglycaemia** is defined as a blood glucose concentration of  $\leq 2.6$  mmol/l, and should always be confirmed in the laboratory

- Hypoglycaemia screen:
  - Glucose
  - Insulin, C-peptide
  - Cortisol
  - Acylcarnitines
  - Lactate
  - Amino acids
  - Free fatty acids:ketones (NEFA:BOHB)
  - Growth hormone
  - Ketones (dipstick urine)
  - Organic acids (urine)

The key additional investigation is the presence or absence of ketosis. Hypoketotic hypoglycaemia has a limited differential diagnosis that can usually be resolved on history and examination:

- Hyperinsulinism (endogenous or exogenous)
- Fat oxidation defects (e.g. MCADD)
- Liver failure
- Mitochondrial disorder

**Hyperinsulinism** is suggested by a persistently increased glucose demand  $>10$  mg/kg/min

$$\text{Glucose requirement (mg/kg/min)} = (\text{ml/h} \times \% \text{ dextrose}) / (6 \times \text{weight in kg})$$

Fasting tolerance may give additional clues:

- $<1$  hour: hyperinsulinism
- $<4$ – $6$  hours: glycogen storage disorders
- $10$ – $20$  hours: gluconeogenesis defects
- $15$ – $24$  hours: fat oxidation defects, ketone synthesis and ketolysis defects

## Lactate

Lactate is a weak acid that can be used directly as a fuel for the brain and is readily produced during anaerobic respiration. Secondary causes of lactate level anomalies (e.g. hypoxia, sepsis, shock, liver failure, poor sampling) are much more common than primary metabolic causes. Ketosis is usually present in primary metabolic disease, unlike in secondary causes, with the exception of pyruvate dehydrogenase deficiency, GSD type I and fat oxidation defects. The level of lactate is unhelpful in distinguishing the cause, and the lactate:pyruvate ratio usually adds little. A low ratio ( $<10$ ) may indicate pyruvate dehydrogenase deficiency. Exacerbation when a patient is fasted is a feature of

gluconeogenesis defects, of GSD type I compared with GSD type III, and of respiratory chain disorders in which lactate may increase postprandially. The markedly raised lactate in decompensated fructose biphosphatase deficiency characteristically resolves rapidly on treating the hypoglycaemia.

Cerebrospinal fluid (CSF) lactate is raised in mitochondrial disorders, central nervous system (CNS) sepsis and seizures.

## Ammonia

Hyperammonaemia may result from poor sampling (squeezed sample) and/or delays in processing. The level of ammonia may prove discriminatory as to the cause.

## Diagnosis from ammonia concentration

Ammonia concentration ( $\mu\text{mol/l}$ )	Differential diagnosis
<40	Normal
40 to <150	Sick patient, fat oxidation defect, OA, liver failure, UCD
150 to <250	Fat oxidation defect, OA, liver failure, UCD
250 to <450	OA, liver failure, UCD
450 to >2000	Liver failure, UCD, (OA rarely)

OA, organic acidaemia; UCD, urea cycle defect.

## Transient hyperammonaemia of the newborn

(THAN) is characterized by very early onset; usually in the first 36 hours before feeding is truly established. It is associated with low glutamine. THAN is managed as other UCDs acutely, but has an excellent prognosis if treated early because hyperammonaemia is secondary to blood bypassing the liver (e.g. patent ductus venosus), rather than a block in the urea cycle.

## Amino acids

Amino acids are measured in both blood and urine. The latter reflects renal threshold, e.g. generalized aminoaciduria of a proximal renal tubulopathy or the specific transporter defect of cystinuria (cystine, ornithine, arginine, lysine). An increase in the serum levels of a specific amino acid may be missed if only a urine sample is analysed and the renal threshold has yet to be breached. Plasma amino acids are useful in the work-up of a number of metabolic disorders, and are essential for monitoring in some:

- $\uparrow$  leucine, isoleucine and valine – MSUD
- $\uparrow$  glutamine,  $\downarrow$  arginine ( $\pm \uparrow$  citrulline) – UCDs
- $\uparrow$  alanine – lactic acidosis

- ↑ glycine – NKH, OAs
- ↑ phenylalanine – phenylketonuria
- ↑ tyrosine – tyrosinaemia

## Organic acids

These are measured in urine only and are diagnostic in many organic acidaemias, e.g. increased propionate in propionic acidaemia, increased isovalerate in isovaleric acidaemia, but are also essential in the diagnosis of other disorders.

- ↑ orotic acid – UCDs, mitochondrial, benign hereditary orotic aciduria
- ↑ methylmalonate – vitamin B<sub>12</sub> deficiency and disorders methylmalonic aciduria
- ↑ succinylacetone – tyrosinaemia type I
- ↑ dicarboxylic acids – fat oxidation defects, medium-chain triglyceride feeds, mitochondrial

## Acylcarnitines

Carnitine conjugates with acyl-CoA intermediates proximal to the block in fat oxidation defects. The chain length of the acylcarnitines formed is diagnostic of where the block lies, e.g. medium-chain (MCAD), very long-chain (VLCAD). Likewise, conjugation with organic acids allows diagnosis of organic acidaemias, e.g. propionylcarnitine. Total and free carnitine levels can be measured at the same time: very low in carnitine transporter defects, low in fat oxidation defects and organic acidaemias, high in carnitine palmitoyltransferase deficiency 1 (CPT1).

## Urate

Urate is the end-product of the breakdown of purines. Raised levels in plasma may indicate increased production (e.g. Lesch–Nyhan syndrome, GSD type I, rhabdomyolysis) or decreased excretion (familial juvenile hyperuricaemic nephropathy or FJHN). It is essential to measure a concurrent urinary urate because urate clearance in children is so efficient that plasma levels may be in the upper normal range in Lesch–Nyhan syndrome, whereas urinary levels are grossly elevated. In FJHN the reverse is true with high plasma urate, but low urinary urate. Low plasma urate is seen in molybdenum cofactor deficiency as a result of a block in the conversion of purine bases to urate.

## Acute patient screening

Specific metabolites are used to screen acute patients for specific disorders or groups of disorders.

## Specific metabolite screens

Metabolite	Disorder
Very-long-chain fatty acids	Peroxisomal disorders, e.g. Zellweger syndrome, adrenoleukodystrophy



Transferrin isoelectric focusing	Congenital disorders of glycosylation
Urate	Purine disorders
7-Dehydrocholesterol	Smith–Lemli–Opitz syndrome
Biotinidase	Biotinidase deficiency
Cardiolipins	Barth syndrome
Creatine and guanidinoacetate (GAA)	Creatine disorders
Urinary glycosaminoglycans and oligosaccharides	Mucopolysaccharidoses and mucopolipidoses
Urinary reducing substances	Galactosaemia
Urinary sulphites	Sulphite oxidase deficiency, molybdenum cofactor deficiency
Urinary AASA (L- $\alpha$ -aminoadipic-semialdehyde)	Pyridoxine-dependent seizures
Urinary purine and pyrimidine metabolites	Purine and pyrimidine disorders

---

Secondary investigations include:

- Neuroimaging: leukodystrophies, mitochondrial disorders, peroxisomal
- Neurophysiology: mitochondrial, peroxisomal, sphingolipidoses
- Echocardiography: especially hypertrophic cardiomyopathy, mitochondrial, fat oxidation, Pompe disease (GSD type II), storage disorders
- ECG: fat oxidation, mitochondrial, Pompe disease
- EEG: metabolic encephalopathy, e.g. MSUD, hyperammonaemia

## Enzymology

Definitive diagnosis is confirmed on enzymology. The sample requirement depends on which tissues express the enzyme, e.g. galactosaemia (blood), OTC deficiency (liver), mitochondrial (muscle). Genotype has superseded invasive biopsy in some conditions, e.g. GSD type I (glucose 6-phosphatase deficiency).

White cell enzymes are often requested in patients with potential neurodegenerative or storage disorders. Laboratories usually undertake different lysosomal assays for different presentations. The neurodegeneration panel includes Tay–Sachs disease, Sandhoff disease, Sly mucopolysaccharidosis (MPS VII) and mannosidosis in plasma;  $G_{M1}$  gangliosidosis, arylsulphatase A deficiency, Krabbe disease and fucosidosis in white cells. The organomegaly panel includes Sly syndrome (MPS VII) and mannosidosis in plasma,  $G_{M1}$  gangliosidosis, Gaucher disease, Niemann–Pick disease A and B, mannosidosis, fucosidosis and Wolman disease in white cells.

## Developmental delay

A screen for metabolic causes of developmental delay has a low yield in unselected patients; 1-3%. However, these are important diagnoses to exclude as there may be specific treatment and the opportunity to prevent further decompensation. It is therefore important to look for clues to help target investigation. Clues from history include the following:

- Pregnancy: maternal health
- Family history: consanguinity
- Past medical: unexplained hypoglycaemia, encephalopathy, protein aversion, self-injurious behaviour, seizure disorder
- Type of delay:
  - Regression
  - Hypotonia
  - Speech delay

## **Metabolic screen for developmental delay**

- Ammonia
- Urate
- Lactate
- Amino acids
- Organic acids (urine)
- Glycosaminoglycans (GAGs) and oligosaccharides (urine)

Specific clues may point to the need for specific investigations.

## **2.5 Acute management**

- Stop feeds
- Promote anabolism – give 10% dextrose with appropriate electrolyte additives (add insulin rather than reduce percentage dextrose if hyperglycaemic). Note that high-concentration glucose can exacerbate the lactic acidosis of pyruvate and respiratory chain defects, so 5% dextrose should be used if primary lactic acidosis is suspected
- Correct biochemical disturbance along standard guidelines, e.g. hypernatraemia, low phosphate etc.
- Clear toxic metabolites:
  - Dialysis – lactate, organic acids, ammonia, leucine
  - Drugs – UCDs: sodium phenylbutyrate, sodium benzoate; OAs: carnitine, glycine
- Supplement enzyme cofactors, e.g. biotin, thiamine, riboflavin

In defects of intermediary metabolism feeds are stopped during intercurrent infections to reduce the metabolic load and glucose polymer drinks are substituted to avoid catabolism. Failure to tolerate the emergency regimen requires admission for intravenous therapy.

## **Pitfalls in management**

- Prolonged cessation of feeds – promotes catabolism. Protein should be withheld for a maximum of 48–72 hours. Restart 0.5 g/kg per day if results still not available
- Hypotonic fluids – risk of hyponatraemic seizures. Ensure dextrose fluids include appropriate sodium and potassium supplementation
- Post-acidosis correction hypokalaemia – ensure close monitoring and correction of potassium during correction of acidosis

## 2.6 Long-term management

Enhance product		
Precursor therapy	Vitamin B <sub>12</sub>	Cobalamin disorders
Enzyme replacement therapy		Gaucher, Fabry, Pompe, Hurler, Hunter, Morquio, Maroteaux, Lamy, Wolman diseases
Supplementary cofactors	Pyridoxine	Homocystinuria
Replace product	Mannose	CDG 1b
	Carnitine	Carnitine transporter defect
	Carbaglu (carglumic acid)	N-Acetylglutamate synthase deficiency
Alternative product	Ketogenic diet	GLUT1 deficiency
Block product clearance	MAO (monoamine oxidase) inhibitor	Aromatic L-amino acid decarboxylase (AADC) deficiency
Product receptor agonist	Dopamine agonist	AADC deficiency
Transplantation	Liver, hepatocyte	UCD, OAs, GSD
	Bone marrow	X-ALD, MPS
Gene therapy (future)		

See text for abbreviations.

Reduce toxicity		
Dietary restriction	Protein	PKU, UCDs, OAs, MSUD
	Fat	VLCAD, LCHAD
	Lactose/galactose	Galactosaemia
Substrate deprivation	Miglustat	Gaucher, Niemann–Pick C, Tay–Sachs diseases
Block production	Nitisinone	Tyrosinaemia
Block site of action	Dextromethorphan	NKH
Enhance removal	Carnitine	OAs
	Sodium benzoate	UCDs
	Sodium phenylbutyrate	UCDs
Transplantation	Liver, hepatocyte	UCD, OAs, GSD
	Bone marrow	X-ALD (X-linked adrenoleukodystrophy), MPS
Gene therapy (future)		

See text for abbreviations.

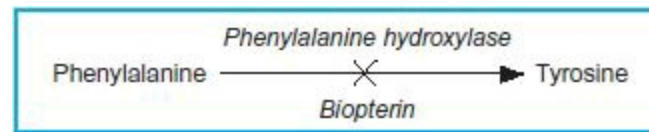
## Genetic counselling

- Risk of recurrence
- Availability of prenatal testing and preimplantation genetic diagnosis (PGD)
- Screen siblings if at risk

## 3. DISORDERS OF AMINO ACID METABOLISM

### 3.1 Phenylketonuria

The most common inborn error of metabolism in the UK; incidence of 1:10 000, carrier rate of 1:50.



## Clinical features

### Untreated classic PKU (phenylalanine >1000 $\mu\text{mol/l}$ )

- Developmental delay in the first year
- Learning disability
- Behavioural problems
- Decreased pigmentation
- Dry skin

### Treated classic PKU

- Asymptomatic
- IQ approximately 10 points below unaffected sibling

One to two per cent result from defects in biotin, which is the essential cofactor for phenylalanine hydroxylase and neurotransmitter synthesis.

## Diagnosis

- Raised phenylalanine level (usually newborn screen)
- Check for biotin defects

## Management

- Phenylalanine restriction (given as exchanges of natural protein titrated against phenylalanine levels, monitored on home fingerprick blood tests)
- Amino acid supplement (no phenylalanine)
- Special PKU products (minimal or no phenylalanine)
- Free foods (negligible phenylalanine)
- Neurotransmitter replacement in biotin defects ( $\pm$  folinic acid)

Phenylalanine is an essential amino acid and therefore cannot be totally excluded from the diet. Patients with milder elevations of phenylalanine, hyperphenylalaninaemia (HPA), require monitoring only. Biotin is licensed but not currently funded in the UK for management of PKU, but is most likely to be effective in HPA.

Phenylalanine is teratogenic and therefore affected girls need strict dietary control pre-conception and during pregnancy to ensure the best outcomes.

### 3.2 Tyrosinaemia (type 1)

Tyrosinaemia type 1 results from a block in the catabolism of tyrosine, producing by-products that damage the liver and kidney.

## Clinical features

- Early onset liver disease with coagulopathy and proximal renal tubulopathy
- Late onset: faltering growth and rickets (secondary to renal Fanconi syndrome); developmental delay
- Development of hepatocellular carcinoma in late childhood/adolescence

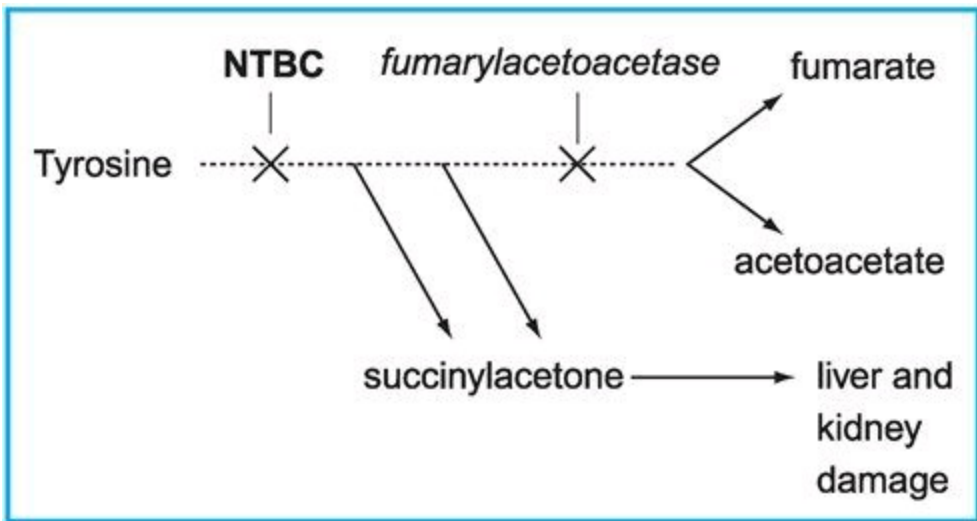
## Diagnosis

- Raised tyrosine
- Organic acids: succinylacetone is pathognomonic
- Deranged clotting (prolonged international normalized ratio or INR)
- Confirmation liver enzymology (fumarylacetoacetase)
- Genotype

## Management

- Tyrosine restricted
- Amino acid supplement (tyrosine free and phenylalanine free)
- Nitisinone blocks catabolic pathway proximal to the production of the damaging metabolites.

Liver transplantation is reserved for patients failing to respond to nitisinone, or those who develop tumours or progressive cirrhotic liver disease. Tumour surveillance includes interval hepatic MRI and monitoring of  $\alpha$ -fetoprotein



### 3.3 Maple syrup urine disease

MSUD results from a block in the degradation of the branched-chain amino acids leucine, isoleucine and valine. MSUD also belongs to the family of organic acidaemias.

#### Clinical features

- Encephalopathy
- Seizures
- Sweet odour (especially nappy) – hence the name

Biochemical disturbance, i.e. acidosis, ketosis, may be minimal, so the diagnosis is often delayed with the illness frequently being attributed to sepsis. Intermittent forms may present at a later age, patients appearing entirely symptom free between bouts. Cerebral oedema is a well-recognized complication during acute episodes.

#### Diagnosis

- Elevated branched-chain amino acids (leucine, isoleucine and valine) plus alloisoleucine
- Elevated branched-chain oxo-acids on urinary organic acids
- Enzymology on fibroblasts

#### Management

- Low-protein diet
- Branched-chain amino acid-free supplement
- Valine and isoleucine may require additional supplementation because levels may fall too low while controlling leucine
- Trial of thiamine (enzyme cofactor)

### 3.4 Homocystinuria

Homocystinuria may result from a number of metabolic defects. Classic homocystinuria (cystathione- $\beta$ -synthase deficiency) presents with a typical dysmorphism similar to Marfan syndrome. Differences include lower IQ, stiff joints, direction of lens dislocation and malar flush in homocystinuria.

#### Clinical features of homocystinuria

- Marfanoid habitus (span greater than height), high arched palate, arachnodactyly
- Restricted joint movements
- Ectopia lentis (classically downward, but may be sideways!)

- Developmental delay/retardation (variable severity)
- Thrombosis (deep vein thrombosis and pulmonary embolus most common)
- Osteoporosis

## Diagnosis

- Elevated homocysteine
- Raised methionine
- Enzymology in fibroblasts

## Management

Treatment aims to reduce plasma total homocysteine to in turn reduce the risks of thrombosis and lens dislocation.

- Protein restriction for patients diagnosed on newborn screening
- Pyridoxine (cofactor) – 50% patients respond
- Folate
- Betaine: lowers homocysteine by remethylation and is particularly useful in the pyridoxine non-responsive patient

## 3.5 Non-ketotic hyperglycinaemia

Defective glycine cleavage produces this early onset seizure disorder. Glycine is a neurotransmitter, excitatory centrally and inhibitory peripherally.

### Clinical features of NKH

- Increased fetal movements (*in utero* seizures)
- Hiccups, hypotonia
- Progressive apnoeas/encephalopathy
- Seizures
- Marked developmental delay/psychomotor retardation

## Diagnosis

- Elevated glycine in urine or plasma
- CSF:plasma glycine ratio ( $>0.09$ )
- Enzymology in liver or lymphocytes

## Management

- Sodium benzoate: reduces plasma glycine, but little effect on neurological outcome

- Dextromethorphan (partial *N*-methyl-D-aspartate or NMDA receptor antagonist): helps block the central action of glycine to reduce fits

Prognosis remains poor for development. Prenatal testing is available.

## 4. ORGANIC ACIDAEMIAS

Defects in the catabolism of amino acids result in the accumulation of organic acids which are detected in urine. Propionic acidaemia (PA) and methylmalonic aciduria (MMA) result from blocks in branched-chain amino acid degradation, isovaleric acidaemia (IVA) is the result of a block in leucine catabolism, and glutaric aciduria type 1 (GA-1) results from a block in lysine and tryptophan metabolism.

### 4.1 Propionic, methylmalonic and isovaleric acidaemias

#### Clinical features of organic acidaemias

- Acute neonatal encephalopathy (intoxication) or chronic intermittent forms
- Dehydration
- Marked acidosis ( $\uparrow$  anion gap), ketosis
- Neutropenia  $\pm$  thrombocytopenia (acute marrow suppression)
- Progressive extrapyramidal syndrome (MMA, PA), basal ganglia necrosis
- Renal insufficiency (MMA)
- Pancreatitis
- Acute-onset cardiomyopathy (PA, MMA)

#### Diagnosis

- Marked metabolic acidosis
- Ketosis
- Raised lactate
- Raised ammonia (secondary urea cycle inhibition)
- Glucose may be low, normal or raised
- Neutropenia
- Urinary organic acids – key metabolites
- Enzymology

Propionate is partly produced by gut organisms, so decompensation in PA and MMA may be precipitated by constipation. Enzyme deficiency is confirmed on enzymology.

#### Management



- Dietary protein restriction
- Carnitine: helps eliminate organic acids via conjugation and renal excretion. Glycine is used similarly in IVA
- Metronidazole (MMA and PA), to alter the gut flora, reduces propionate production and helps avoid constipation
- Some forms of MMA are vitamin B<sub>12</sub> responsive
- Liver transplantation (PA, MMA) does not completely eliminate the risk of neurological deterioration

## 4.2 Glutaric aciduria type 1

### Clinical features of glutaric aciduria type 1

Before decompensation:

- Asymptomatic
- Macrocephaly/frontal bossing

After decompensation (usually precipitated by an intercurrent infection), usually occurring towards the end of the first year:

- Encephalopathy
- Dystonia/choreoathetosis
- Feeding problems (oral dystonia)
- Irritability

### Diagnosis

- Raised 3-hydroxyglutarate, glutarate in organic acids
- Raised glutarylcarntine
- MRI of the brain: frontal atrophy, subdural haematomas, decreased signal for basal ganglia
- Enzymology on fibroblasts
- Genotyping

The diagnosis must be actively sought in children with large heads and no other explanation, in an effort to prevent metabolic decompensation and subsequent severe neurology.

GA-1 may mimic non-accidental injury with encephalopathy and bilateral subdurals.

### Management

- Carnitine
- Protein restriction (low lysine diet)

- Aggressive treatment of infections
- Hyperalimentation and use of the emergency regimen (glucose polymer) when unwell

## 5. UREA CYCLE DEFECTS

The urea cycle is the pathway by which waste nitrogen is converted to urea for disposal. UCDs are inherited in an autosomal recessive manner except OTC deficiency, which is X-linked recessive. Girls may present symptomatically if during lyonization sufficient good genes are switched off in the liver.

### Clinical features of UCDs

- Vomiting (may be a cause of cyclical vomiting)
- Encephalopathy (intoxication after symptom-free period in neonate)
- Tachypnoea (ammonia is a respiratory stimulant acting centrally)
- Progressive spastic diplegia and developmental delay (arginase deficiency)
- Arginase deficiency rarely presents with classic hyperammonaemia

### Diagnosis

UCDs are suggested by the presence of a respiratory alkalosis in the child with encephalopathy. Indication of the exact level of the enzyme block depends on plasma amino acids and urinary organic acids for the presence or absence of orotic acid. Orotic aciduria indicates a block at the level of OTC or beyond. Final confirmation of the diagnosis requires enzymology.

### Characteristics of urea cycle defects

Urea cycle defect	Enzyme deficiency	Amino acids	Orotic acid
N-Acetylglutamate synthase deficiency	N-Acetylglutamate synthase	Glu ↑, Arg ↓ Cit ↓	Normal
Carbamyl phosphate synthase deficiency	Carbamyl phosphate synthase	Glu ↑, Arg ↓ Cit ↓	Normal
Ornithine transcarbamylase deficiency	Ornithine transcarbamylase	Glu ↑, Arg ↓ Cit ↓	↑↑↑
Citrullinaemia	Argininosuccinic synthase	Glu ↑, Arg ↓ Cit ↑↑↑	↑
Argininosuccinic aciduria	Argininosuccinic lyase	Glu ↑, Arg ↓ Cit ↑	↑
Argininaemia	Arginase	Argininosuccinate ↑ Glu ↑, Arg ↑↑↑	↑

Arg, arginine; Cit, citrulline; Glu, glutamine.

### Management

- Protein restriction
- Sodium benzoate and sodium phenylbutyrate conjugate with glycine and glutamine, respectively, to produce water-soluble products that can be excreted by the kidney, therefore bypassing the urea cycle and reducing the nitrogen load on the liver
- Arginine supplementation (an essential amino acid in UCDs – except arginase deficiency)
- Liver transplantation in patients with brittle control

## 6. FAT OXIDATION DISORDERS

The fat oxidation defects form a large group of conditions that commonly present with hepatic, cardiac or muscle symptoms. Fatty acids are a major fuel source in the fasted state and are oxidized by most tissues except the brain, which is reliant on hepatic fatty acid  $\beta$ -oxidation for ketone production. Fatty acids are the preferred substrate for cardiac muscle, and during prolonged exercise they are a vital energy source for skeletal muscle.

### 6.1 Medium-chain acyl-CoA dehydrogenase deficiency

MCADD is the most common fat oxidation disorder in the UK with an incidence of 1 in 10 000 (as common as PKU). Peak presentation in unscreened patients occurs in autumn and winter precipitated by intercurrent infections. The mortality rate is 25% on first presentation in clinically presenting (unscreened) patients, with 13% of survivors having neurological sequelae.

#### Clinical features of MCADD

- Hypoketotic hypoglycaemia
- Encephalopathy
- Reye syndrome-like syndrome: hepatomegaly, deranged liver function
- Mean age at presentation 15 months; most common precipitant is diarrhoea
- Sudden infant death (consider in older infant >6 months)
- Common G985 mutation

#### Diagnosis

- Hypoglycaemia with absent or low ketones
- Raised octanoylcarnitine (C8 carnitine) on acylcarnitines
- Raised hexanoylglycine in urinary organic acids
- Genotyping

Newborn screening for MCADD is undertaken in England, Scotland and Northern Ireland.

#### Management

- Avoidance of fasting
- If unwell, emergency regimen drinks (glucose polymer). If not tolerated intravenous 10% dextrose with electrolyte additives (sodium and potassium)

In the at-risk neonate born to a family with a previously affected sibling, feeds should be frequent with intervals no longer than 3 hours, and top-up feeds established if needed while acylcarnitine

results are awaited. Neonatal deaths have been reported.

## 6.2 Long-chain defects

The long-chain fat oxidation defects, VLCAD and LCHAD are more severe, presenting at an earlier age and requiring meticulous dietary management to ensure normoglycaemia and to reduce long-term complications. Liver dysfunction may occur in the carrier mother during pregnancy: AFLP or HELLP syndrome.

### Clinical features of long-chain defects

- Hypoketotic hypoglycaemia
- Myopathy
- Hypertrophic cardiomyopathy
- Pigmentary retinopathy (LCHAD)
- Peripheral neuropathy (LCHAD)
- Maternal hepatic symptoms in pregnancy

### Diagnosis

- Hypoketotic hypoglycaemia
- Characteristic long-chain acylcarnitines
- Characteristic dicarboxylic aciduria in urinary organic acids
- Raised creatine kinase (risk of rhabdomyolysis)
- Fat oxidation studies on fibroblasts
- Genotyping (common LCHAD mutation)

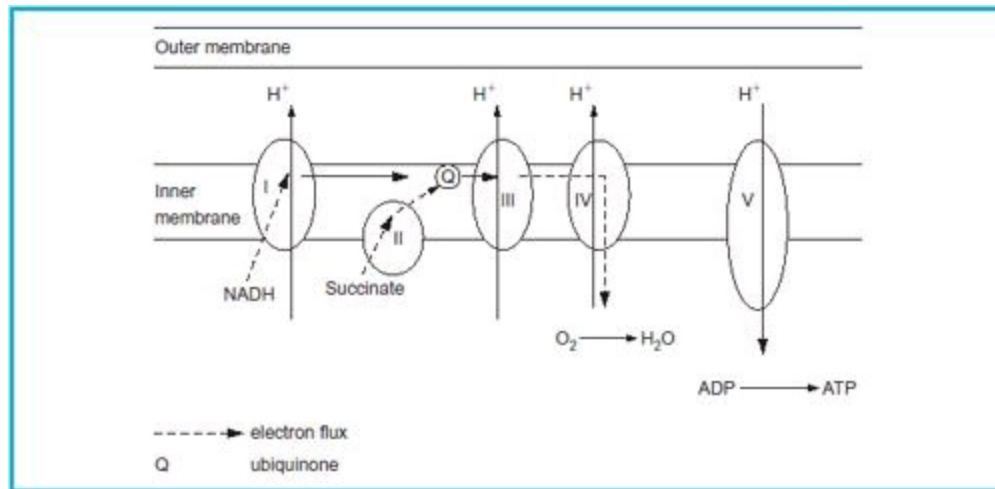
Acylcarnitines should be checked in infants born to mothers with AFLP or HELLP syndrome.

### Management

- Long-chain fat restriction
- Essential fatty acid supplementation (walnut oil)
- Avoidance of fasting – frequent bolus feeds during the day, and overnight nasogastric or gastrostomy feeds in infancy
- Uncooked cornstarch can be introduced from 2 years of age to smooth and prolong glycaemic control
- An emergency regimen is used during intercurrent infections with admission for intravenous therapy if not tolerated

## 7. MITOCHONDRIAL DISORDERS

Mitochondria are the power stations of the cell, producing ATP to drive cellular functions. The respiratory chain, the site of oxidative phosphorylation, is embedded in the inner mitochondrial membrane and consists of five complexes (See figure opposite). Electrons are donated from reduced cofactors (NADH, FADH<sub>2</sub>) and passed along the chain, ultimately reducing oxygen to water, while the energy so produced pumps hydrogen ions from the mitochondrial matrix into the intermembrane space. Discharge of this electrochemical gradient through complex V (ATP synthase) generates ATP.



## 7.1 Mitochondrial genetics

Mitochondria are unique in containing their own DNA (mtDNA), contained within a circular double-stranded molecule. The mtDNA is inherited solely from the maternal egg, the sperm's mitochondria being left outside within the tail at fertilization. Inheritance of mtDNA point mutations is therefore matrilineal, only being handed on by females although males and females are affected. However, the mitochondrion is not self-sufficient but relies on nuclear genes for many essential proteins, including respiratory chain subunits. Approximately 10% of all nuclear genes are involved in the production and maintenance of healthy mitochondria. All complex II subunits are encoded within the nucleus. If a nuclear gene is at fault then normal mendelian inheritance applies. Autosomal recessive inheritance is probably the most common mode of inheritance for paediatric practice.

Mitochondria also contain more than one copy of mtDNA, and each cell may contain many mitochondria. It is possible to have mutant and wild-type mtDNA present in the same cell (heteroplasmy). The accumulation of mutant mtDNA will result in symptoms when a threshold is breached. As a result of heteroplasmy, symptoms may be patchy within and between organ systems. In rapidly dividing cells, such as the bone marrow and gut, wild-type cells may have a reproduction advantage and therefore symptoms in these organ systems may improve compared with the progressive brain and muscle involvement. Unless a nuclear defect is identified, prenatal diagnosis is not available. It is hoped that newer genetic techniques such as next generation sequencing and whole exome sequencing will allow rapid genotyping in these patients.

Nuclear defects may result in reduction in qualitatively normal mtDNA – the mitochondrial depletion syndromes, e.g. *POLG*, *DGUOK* and *TK2* genes.

## 7.2 Clinical features

As mitochondria are present in all cells except erythrocytes, any organ system can be involved at any time with any inheritance. High-energy-demand tissues are more commonly involved, particularly brain, muscle, heart, kidney and liver, but any system can be involved. Thirty-three per cent of children present in the neonatal period, and 80% in the first 2 years. Many syndromes have been described; however, these were initially reported in adults and are associated with mtDNA mutations that are less common in children (e.g. mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes [MELAS], myoclonic epilepsy–ragged red fibres [MERRF] and Kearns–Sayre syndrome). Syndromes may also be incomplete.

- CNS: Leigh syndrome, hypotonia, deafness, epilepsy, stroke-like episodes
- Muscle: myopathy, fatigue
- Heart: hypertrophic cardiomyopathy, heart block
- Kidney: proximal tubulopathy
- Liver: failure, cirrhosis
- Gut: diarrhoea, malabsorption, pancreatic insufficiency, faltering growth
- Eye: external ophthalmoplegia, pigmentary retinopathy
- Bone marrow: refractory anaemia
- Endocrine: short stature, diabetes, endocrinopathies

## Investigation

Studies of mtDNA are preferred if a classic mitochondrial syndrome is identified. Preferred tissue is either muscle or bladder cells (extracted from a urine specimen). Blood may be less reliable as the mutant load may decrease with time. Usually mitochondrial disease is suspected when there is multiorgan involvement in apparently unrelated organs – so-called ‘illegitimate associations’. Peripheral lactate may be persistently elevated. Further organ involvement may be sought before muscle biopsy for histochemistry (staining for complex II and IV), and respiratory chain enzymology: complexes I–IV + V.

- CNS: MRI, brain-stem auditory evoked potentials, CSF lactate
- Heart: echocardiography, electrocardiogram (ECG)
- Kidney: proximal tubular proteins, tubular resorption of phosphate
- Liver: biopsy, enzymology
- Gut: stool elastase
- Eye: fundoscopy, electroretinogram (ERG), visual evoked responses
- Marrow: full blood count (FBC), aspirate
- Endocrine: electrolytes

## Management

Management remains supportive. A variety of antioxidants and respiratory-chain pick me ups have been described with success in only a handful of cases, e.g. ubiquinone, riboflavin. Dichloroacetate

resolves the raised lactate but does not appear to improve outcome. Graded exercise has been used in some patients with myopathy.

## 8. DISORDERS OF CARBOHYDRATE METABOLISM

### 8.1 Glycogen storage disease

Glucose is stored in the liver, muscles and kidneys as glycogen. GSDs result from defects of glycogen breakdown. Hepatic forms present with hepatomegaly and hypoglycaemia, the muscle forms present with weakness and fatigue.

#### **GSD Ia (glucose-6-phosphatase deficiency – von Gierke disease)**

The enzyme deficiency fails to remove the phosphate from glucose 6-phosphate, so export of glucose from the liver through glycogenolysis and gluconeogenesis is blocked. Fasting tolerance is therefore limited, usually 1–4 h. Infants usually present at around 3 months when feeds are spread further apart.

#### **Clinical features**

- Massive hepatomegaly (in the absence of splenomegaly). Glycogen is not stored in the spleen, unlike the material in lysosomal storage disorders
- Abnormal fat distribution (doll-like faces and thin limbs)
- Failure to thrive
- Bruising (secondary to poor platelet function)
- Nephromegaly common

Long-term complications include renal insufficiency, liver adenomas with potential for malignant change, gout, osteopenia and polycystic ovaries.

#### **Investigations**

- Hypoglycaemia
- Raised plasma lactate. Lactate levels fall on glucose loading
- Hyperuricaemia
- Hyperlipidaemia
- Genotyping has superseded liver enzymology for confirmation

#### **Treatment**

- Frequent feeds during the day with continuous feed overnight. From age 2, uncooked cornstarch is introduced as a slow-release form of glucose, prolonging the gap between feeds
- Allopurinol to control the uric acid level in the blood
- Liver transplantation is reserved for patients with malignant change in an adenoma or failure to

respond to dietary treatment

## **GSD Ib (glucose-6-phosphate translocase deficiency)**

The translocase deficiency shares the above phenotype with the addition of neutrophil dysfunction, with associated recurrent skin sepsis, large mouth ulcers and inflammatory bowel disease. Management is as above with the addition of prophylactic Septrin (co-trimoxazole) for severe recurrent mouth ulcers, or granulocyte colony-stimulating factor (GCSF) in resistant cases.

## **GSD II (Pompe disease)**

GSD II, acid maltase deficiency, is really a lysosomal storage disorder with accumulation of glycogen in lysosomes. The infantile form presents with severe hypotonia, weakness, hyporeflexia and a large tongue. ECG reveals giant QRS complexes. Vacuolated lymphocytes are seen on the blood film. Confirmatory enzymology is performed on fibroblasts. Death is usual within the first year; however, enzyme replacement therapy trials have shown encouraging results. Milder forms with mainly myopathy exist.

## **GSD III (debrancher enzyme)**

**Type IIIa** affects liver and muscle, whereas **type IIIb** is purely hepatic. Type III may be clinically indistinguishable from type I; however, fasting tolerance is longer because gluconeogenesis is not blocked, and glycogen can be pruned to near the branch points. Nephromegaly is not a feature. Myopathy is notable and may be progressive in type IIIa. Cardiomyopathy is a complication, but usually clinically insignificant. Adenomas, liver fibrosis and cirrhosis are rare.

Lactate level rises, unlike in type I, on glucose loading. The diagnosis may be confirmed on white cell enzymology. Dietary management is similar to but not as intensive as for type I. A high protein diet has been suggested for the type IIIa.

## **GSD IV (branching enzyme)**

This form is very rare and presents with hepatomegaly and progressive liver disease. The diagnosis is usually made on liver histology and enzymology. Liver transplantation is the treatment for progressive disease.

## **GSD VI (liver phosphorylase deficiency) and GSD IX (phosphorylase-b-kinase deficiency)**

Hypoglycaemia is rarely a problem. Hepatomegaly may be an incidental finding. GSD IX enzymology is assayed in red cells but may be normal in the isolated liver form. Treatment consists of uncooked cornstarch once or twice a day to aid growth. Inheritance is X-linked or recessive depending on subgroup.



# Muscle GSDs

## GSD V (muscle phosphorylase deficiency), McArdle disease and GSD VII (phosphofructokinase deficiency)

Weakness and fatigue with post-exercise stiffness are the presenting features. Serum creatine kinase is usually elevated along with uric acid. On exercise, lactate fails to rise with excessive increases in uric acid and ammonia. After a brief rest, exercise can be restarted ('second-wind') as fatty acids slowly become available as an alternative fuel. Protein in the diet may be beneficial. Glucose is of benefit in McArdle disease because glycolysis is still intact. Extreme exercise should be avoided but regular gentle exercise is probably of benefit.

## 8.2 Galactosaemia

### Clinical features of galactosaemia

- Neonatal onset – jaundice, hepatomegaly, coagulopathy and oil-drop cataracts, usually at the end of the first week
- Later presentation with faltering growth, proximal tubulopathy and rickets at a few months
- Association with *Escherichia coli* sepsis

### Diagnosis

- Reducing substances in the urine (rapidly disappear if feeds stopped)
- Deranged liver function including prolonged INR
- Gal-1-PUT (galactose-1-phosphate uridyltransferase) assay. If the child has already received a transfusion, the parents should be screened for carrier-level activity instead

### Management

- Lactose-/galactose-free diet
- Ensure adequate calcium intake. Milk is replaced with a soya-based formula

Long-term complications, in spite of good control, include developmental delay, particularly involving speech, feeding problems and infertility in girls.

## 8.3 Hereditary fructose intolerance

The key to diagnosis is the linking of symptoms with the exposure to fructose, which usually occurs at weaning.

### Clinical features of hereditary fructose intolerance

- Acute – vomiting and symptomatic hypoglycaemia
- Chronic exposure – faltering growth, hepatomegaly, ascites, jaundice and proximal renal tubulopathy
- Milder cases – learn to avoid sugary foods
- Exacerbations may occur AFTER exposure to fructose contained in medicines

## Diagnosis

- History
- Lactic acidosis
- Hyperuricaemia
- Deranged liver function
- Aldolase B activity in liver
- Genotyping is used when liver biopsy is contraindicated because of coagulopathy

## Management

Lifelong avoidance of fructose.

## 9. LIPID DISORDERS

Cholesterol and triglycerides are transported in the circulation bound to lipoproteins.

The four major classes are:

- **Chylomicrons**: carry dietary lipids, mainly triglycerides, from the gut to the liver. Lipoprotein lipase releases free fatty acids from chylomicrons in the portal circulation
- **Very-low-density lipoprotein (VLDL)**: carries predominantly triglycerides and some cholesterol synthesized in the liver to the peripheries. Lipoprotein lipase releases the free fatty acids leaving IDL (**intermediate-density lipoprotein**)
- **Low-density lipoprotein (LDL)**: transports cholesterol and some triglyceride from the liver to the peripheries. Direct uptake by cells via the LDL receptor
- **High-density lipoprotein (HDL)**: carries cholesterol from the peripheries to the liver. Inverse association with ischaemic heart disease (‘good cholesterol’)

### 9.1 Hypertriglyceridaemias

- Defective chylomicron removal – lipoprotein lipase deficiency, apolipoprotein C-II deficiency
- Overproduction of VLDL – familial hypertriglyceridaemia

Hypertriglyceridaemias are rare. Clinical features include colic, hepatosplenomegaly, eruptive xanthomas and creamy plasma. Complications include abdominal pain and pancreatitis but rarely

develop in patients until the triglyceride level exceeds 20 mmol/l. Secondary causes of elevated triglycerides include obesity, chronic renal failure, diabetes mellitus and liver disease. Treatment comprises a very-low-fat diet supplemented with essential fatty acids. Drugs used to lower triglycerides include fibric acid derivatives, niacin or statins. Fibrate drugs reduce hepatic triglyceride synthesis and enhance peripheral triglyceride clearance; statins reduce triglycerides, probably by reducing VLDL synthesis.

## 9.2 Hypercholesterolaemias

### Defective LDL removal – familial hypercholesterolaemia

Familial hypercholesterolaemia is a monogenic disorder with a heterozygote incidence of 1:500, and homozygote 1:1000 000. It is the most common hyperlipidaemia, resulting from mutations in the LDL receptor, Apo B or *PCSK9* gene. Patients are picked up through premature ischaemic heart disease, or through cascade screening for hypercholesterolaemia after diagnosis in a relative – usually at least 5 years old. Family history is an important risk factor for ischaemic heart disease, particularly at a young age and especially in girls. In homozygotes, xanthomas may appear in the first decade, and angina before the age of 20.

In children, diet and exercise are the mainstay of treatment, see the NICE (National Institute for Health and Clinical Excellence) guideline ([www.nice.org.uk/CG71](http://www.nice.org.uk/CG71)).

#### Dietary management

- Total fat intake  $\leq 30\%$  total calories
- Saturated fat intake  $\leq 10\%$  total calories (increased mono- and polyunsaturated fats)
- Cholesterol intake  $< 300$  mg
- Fruit and vegetables ‘5 a day’
- Fish twice a week

Smoking is strongly discouraged as is excessive alcohol intake. Statins are usually reserved for children aged 10 years or above. The decision to treat should consider family history, comorbidities, e.g. hypertension, age and LDL-cholesterol concentration. Their mechanism of action is the competitive inhibition of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting step of cholesterol synthesis. Statins are teratogenic and so effective contraception must be used in young women using statins. Patients who are unable to tolerate statins should be offered other lipid-modifying treatment including bile acid sequestrants (statins), fibrates or ezetimibe. Liver function and creatine kinase are regularly monitored for adverse effects. Lipid-modifying drugs are used before plasma apheresis in patients who are homozygous.

### Familial combined hyperlipidaemia

Patients present with hypercholesterolaemia or hypetriglyceridaemia or both. Diagnosis is confirmed by the finding of a first degree relative who has a different biochemical phenotype. The genetics is

unknown. Management includes healthy lifestyle (diet and exercise) with usually a statin in combination with fibrate or nicotinic acid.

## 9.3 ABETALIPOPROTEINAEMIA

Rare autosomal recessive disorder with undetectable apoenzyme B (Apo B) levels and resultant fat malabsorption including fat-soluble vitamins.

### Clinical features

- Poor weight gain
- Steatorrhoea
- Ataxia, neuropathy and other CNS symptoms
- Retinitis pigmentosa

### Investigations

- Hypocholesterolaemia
- Acanthocytes (blood film)
- Low vitamins A, D, E and K

### Management

- Reduced fat intake (5–20 g/day)
- Essential fatty acid supplement (walnut oil)
- Fat-soluble vitamin supplementation

## 10. PEROXISOMAL DISORDERS

Peroxisomes harbour many vital cellular functions, including the synthesis of plasmalogens, (essential constituents of cell walls), cholesterol and bile acids, and the  $\beta$ -oxidation of very-long-chain fatty acids and breakdown of phytanic acid (vitamin A) and glyoxylate. Disorders are biochemically characterized by the number of functions impaired:

- Multiple enzymes affected (peroxisomal biogenesis defects): Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), infantile Refsum disease (IRD)
- Several enzymes involved – rhizomelic chondrodysplasia punctata (RCDP)
- Single enzyme block – X-linked adrenoleukodystrophy (X-ALD), Refsum disease, hyperoxaluria

Inheritance is autosomal recessive with the exception of X-ALD. The first-line investigation is very-long-chain fatty acids that are elevated in ZS and X-ALD but normal in RCDP. In this group, plasmalogens are the first screen. Further investigation requires fibroblast studies.

## 10.1 Zellweger syndrome

ZS is the classic peroxisomal biogenesis disorder with distinctive dysmorphic features. There is clinical overlap with NALD and IRD, which are milder with better prognosis.

### Clinical features of Zellweger syndrome

- Dysmorphic faces – prominent forehead, hypertelorism, large fontanelle
- Severe neurological involvement including hypotonia, seizures and psychomotor retardation
- Sensorineural deafness
- Ocular abnormalities – retinopathy, cataracts
- Hepatomegaly and liver dysfunction
- Calcific stippling (especially knees and shoulders)
- Faltering growth

### Diagnosis

Loss of all peroxisomal functions – raised very-long-chain fatty acids, phytanate and bile acid intermediates and decreased plasmalogens. Confirmatory enzymology on fibroblasts.

### Treatment

Management is supportive. Docosahexaenoic acid supplementation has been tried but no clear benefit has been demonstrated. Death usually occurs within the first year.

## 10.2 X-linked adrenoleukodystrophy

The paediatric cerebral form presents with severe neurological degeneration, usually between age 5 and 10 years, progressing to a vegetative state and death within a few years. Brothers in the same family may present at different ages.

### Clinical features of X-ALD

- School failure, behaviour problems
- Visual impairment
- Quadriplegia
- Seizures (late sign)
- Adrenal insufficiency

Adrenal involvement may precede or follow neurological symptoms by years. Some develop only neurological symptoms, and others just have adrenal insufficiency. All boys developing adrenal

failure should have very-long-chain fatty acid measurements taken to ensure that the diagnosis is not missed. Neurological symptoms may occur for the first time in adults (adrenomyeloneuropathy), resembling a cord syndrome with spastic gait and bladder involvement. Female carriers may develop multiple sclerosis-like symptoms in adulthood.

### Diagnosis

Elevated very-long-chain fatty acids, blunted Synacthen response or frank hypoglycaemia. Neuroimaging shows bilateral, predominantly posterior, white-matter involvement. The differential diagnosis for neurodegeneration in the school-age child includes:

- subacute sclerosing panencephalitis
- Batten disease
- Wilson disease
- Niemann–Pick C disease

### Management

Lorenzo oil (oleic and erucic acid) normalizes the very-long-chain fatty acids but fails to prevent progression. Bone marrow transplantation is the mainstay of therapy in patients before neurodegeneration, i.e. prospectively diagnosed siblings, and those diagnosed after presentation with adrenal insufficiency or other problems. Serial psychometry/neurophysiology and neuroimaging are used to detect the first signs of neurological deterioration – the stimulus for transplantation. Adrenal function should be closely monitored, and steroid replacement therapy should be given once it is indicated.

## 11. MUCOPOLYSACCHARIDOSES

Mucopolysaccharides (glycosaminoglycans) are structural molecules integral to connective tissues such as cartilage. Degradation occurs within lysosomes, requiring specific enzymes. Patients with MPSs appear normal at birth and usually present with developmental delay in the first year. The features of storage become more obvious with time.

### 11.1 Classification

Type	Disorder	Inheritance	Corneal clouding	Skeleton	Hepato-splenomegaly	Learning disability
I	Hurler syndrome	AR	+	+++	+++	+++
II	Hunter syndrome	X-linked	–	+++	+++	+++
III	Sanfillipo syndrome	AR	+	+	+	+++
IV	Morquio syndrome	AR	+	+++	+	–
VI	Maroteaux-Lamy syndrome	AR	+	+++	+++	–
VII	Sly syndrome	AR	+	+++	+++	+++

AR, autosomal recessive.

Hurler syndrome is the classic MPS with storage affecting the body and CNS. Sanfillipo syndrome predominantly affects the CNS and Morquio and Maroteaux–Lamy syndromes affect the body. Atlantoaxial instability is common in the latter two, often necessitating prophylactic cervical spinal fusion in the first 2–3 years. Hunter syndrome is phenotypically similar to Hurler syndrome; however, there is no corneal clouding and scapular nodules are seen.

## 11.2 Hurler syndrome

Hurler syndrome typifies the MPS group and their associated clinical problems. The enzyme deficiency is  $\alpha$ -iduronidase, a deficiency shared with Scheie disease, the milder variant.

### Clinical features of Hurler syndrome

- Coarse faces, macroglossia, hirsutism, corneal clouding
- Airway/ear, nose, throat problems, secretory otitis media
- Dysostosis multiplex
- Cardiomyopathy, valvular disease
- Hepatosplenomegaly
- Hernias – umbilical, inguinal, femoral
- Stiff joints
- Developmental delay and retardation

### Diagnosis

Urinary screen for glycosaminoglycans (raised dermatan and heparan sulphate). Enzymology confirmed on white cells.

### Management

Treatment depends on early recognition to allow early bone marrow transplantation, which significantly modifies the phenotype. Enzyme replacement therapy (ERT) is available; however, blood–brain barrier penetration is limited, so the neurological features are less responsive. Supportive care is the mainstay of untransplanted patients, with particular regard to the chest and airway including regular sleep studies.

## 12. SPHINGOLIPIDOSES

Sphingolipids are complex membrane lipids. They are all derived from ceramide and can be divided into three groups: cerebrosides, sphingomyelins and gangliosides. Lysosomal hydrolases break these molecules down; deficiencies result in progressive storage and disease. Typical features include psychomotor retardation, neurological degeneration including epilepsy, ataxia and spasticity, with or without hepatosplenomegaly.

## 12.1 Tay–Sachs disease

### Clinical features of Tay–Sachs disease

- Developmental regression within first year
- Macrocephaly
- Hyperacusis
- Cherry-red spot
- Spastic quadriplegia
- Death within 2–4 years
- No hepatosplenomegaly compared with Sandhoff disease

### Diagnosis

The presence of vacuolated lymphocytes on the blood film is a further clue. Hexosaminidase A deficiency is confirmed on white cell enzymology.

### Management

Currently, management is supportive. However, research into substrate-deprivation therapy, chaperone therapy and other treatments is currently under investigation.

## 12.2 Gaucher disease

Glucocerebrosidase deficiency results in the accumulation of cerebroside in the visceral organs ± the brain depending on the type.

### Clinical features of Gaucher disease

#### *Type 1*

- Non-neuropathic (most common – 80–90% cases)
- Splenomegaly > hepatomegaly
- Anaemia, bleeding tendency
- Skeletal pain, deformities, osteopenia
- Abdominal pain (splenic infarcts)

#### *Type 2*

- Acute neuropathic
- Severe CNS involvement (especially bulbar), rapidly progressive



- Convergent squinting and horizontal gaze palsy
- Hepatosplenomegaly

### ***Type 3***

- Subacute neuropathic
- Convergent squint and horizontal gaze palsy (early sign)
- Splenomegaly > hepatomegaly
- Slow neurological deterioration

## **Diagnosis**

Elevated angiotensin-converting enzyme (ACE) and acid phosphatase are markers for the disease. Bone marrow aspiration may reveal Gaucher cells (crumpled tissue-paper cytoplasm). White cell enzymes for glucocerebrosidase give the definitive diagnosis. The enzyme chitotriosidase is markedly elevated and may be used to follow disease activity.

## **Management**

ERT is effective in visceral disease in types 1 and 3. Bone marrow transplantation has been used in the past, and may have benefit for cerebral involvement in type 3. Splenectomy has been used to correct thrombocytopenia and anaemia and relieve mechanical problems, but may accelerate disease elsewhere. There is no effective treatment for type 2.

## **12.3 Niemann–Pick disease**

Niemann–Pick disease is the eponymous name for the sphingomyelinoses; however, types A and B are biochemically and genetically distinct from type C.

## **Sphingomyelinase deficiency**

### **Clinical features of sphingomyelinase deficiency**

#### ***Type A (infantile)***

- Feeding difficulties
- Hepatomegaly > splenomegaly
- Cherry-red spot
- Lung infiltrates
- Neurological decline, deaf, blind, spasticity
- Death within 3 years

#### ***Type B (visceral involvement)***

- Milder course, no neurological involvement
- Hepatosplenomegaly
- Pulmonary infiltrates
- Ataxia
- Hypercholesterolaemia

## Diagnosis

Bone marrow aspirate for Niemann–Pick disease cells. White cell enzymes. Genotyping may help distinguish between the two types before the onset of neurological signs.

## Management

Supportive. ERT for Niemann–Pick disease type B is undergoing clinical trials.

## Lysosomal cholesterol-export defect (secondary sphingomyelin accumulation)

### Clinical features of lysosomal cholesterol-export defect

<p><i>Type C</i></p> <ul style="list-style-type: none"> <li>• Conjugated hyperbilirubinaemia (earliest sign)</li> <li>• Hepatosplenomegaly</li> <li>• Neurological deterioration (variable age of onset)</li> <li>• Dystonia</li> <li>• Cherry-red spot</li> <li>• Vertical ophthalmoplegia</li> </ul>
--

## Diagnosis

Niemann–Pick disease cells on bone marrow aspirate; however, white cell enzymes show normal or mildly decreased sphingomyelinase deficiency. Definitive diagnosis requires cholesterol studies on fibroblasts and genotyping.

## Management

Supportive. Miglustat, substrate deprivation therapy, has been shown to delay the onset of neurological symptoms. Prognosis is guided by age of onset.

## 12.4 Fabry disease

$\alpha$ -Galactosidase deficiency results in the storage of glycolipids in blood vessel walls, heart, kidney and autonomic spinal ganglia. It is X-linked recessive. Increasingly, female carriers with symptoms

are being recognized.

Clinical features of Fabry disease
<ul style="list-style-type: none"><li>• Severe pain in extremities (acroparaesthesia)</li><li>• Angiokeratoma (bathing-trunk area)</li><li>• Corneal opacities</li><li>• Cardiac disease</li><li>• Cerebrovascular disease</li><li>• Nephropathy</li><li>• Normal intelligence</li></ul>

## Diagnosis

Maltese crosses (birefringent lipid deposits) in urine under microscope. White cell enzymes.

## Management

ERT now reduces pain and stabilizes renal function.

## 13. MISCELLANEOUS

### 13.1 Porphyria

Porphyrias are a group of disorders of haem biosynthesis that present with acute symptoms and/or skin symptoms. Inheritance is autosomal dominant except in congenital  $\delta$ -aminolaevulinic acid (ALA) dehydratase deficiency, erythropoietic porphyria and hepatoerythropoietic porphyria. Symptoms in children are extremely rare.

### Classification

- Hepatic:
  - Plumboporphyria
  - Acute intermittent porphyria (AIP)
  - Porphyria cutanea tarda (PCT)
  - Hereditary coproporphyria (HCP)
  - Variegate porphyria (VP)
- Erythropoietic:
  - Congenital erythropoietic porphyria (CEP)
  - Erythropoietic protoporphyria (EPP)

### Clinical features of porphyria

## Acute symptoms

Autosomal dominant with poor penetrance. Attacks more common in girls but rare before puberty. Periods of remission. Attacks precipitated by environmental factors: drugs, alcohol, stress, infection, smoking, reduced caloric intake. Severe pain is usually abdominal but may be back or legs. Attacks lasts no more than 1–2 weeks.

- Neurovisceral: AIP, plumboporphyria
  - Neurological: pain, muscle weakness, paralysis, fits, mental changes
  - Gastrointestinal: abdominal pain, vomiting, constipation, diarrhoea
  - Cardiovascular: tachycardia, hypertension
- Neurovisceral + skin: HCP, VP
  - Above + skin

## Treatment of acute attack

- Remove precipitating factor
- Supportive treatment with drugs known to be safe:
  - Pain – opiates
  - Psychosis – chlorpromazine
  - Tachycardia, hypertension –  $\beta$  blockers
  - Seizures – gabapentin, vigabatrin
- Carbohydrate (10% dextrose) switches of ALA synthase induction
- Haem arginate (negative feedback on ALA synthase)
- Skin symptoms: CEP, PCT:
  - Skin: blisters, scarring, pigmentation, fragility, hirsutism
  - Photosensitivity: EPP

Cutaneous forms are managed by avoidance of precipitants, especially sunlight, and good skin care.

## Diagnosis

- Acute attacks (neurovisceral):
  - Raised urinary porphobilinogen during attacks (fresh urine)
  - Faecal and urinary porphyrin analysis to distinguish type
- Skin lesions:
  - Porphyrins urine, faeces, blood
- Photosensitivity:
  - Protoporphyrin (blood)

## 13.2 Smith–Lemli–Opitz syndrome

The Smith–Lemli–Opitz (SLO) syndrome is the most common sterol biosynthesis defect – a group of disorders characterized by limb defects, major organ dysplasia and skin abnormalities.

---

## Clinical features of Smith–Lemli–Opitz syndrome

- Dysmorphic faces – microcephaly, narrow frontal area, upturned nose, ptosis
- Syndactyly of second and third toes
- Genital anomalies
- Learning disability
- Renal anomalies
- Faltering growth
- Feeding difficulties
- Sunlight sensitivity

## Diagnosis

SLO syndrome is the result of a block in the penultimate step of cholesterol biosynthesis, so cholesterol is low with a raised 7-dehydrocholesterol level, the immediate precursor.

## Management

Management is supportive. Cholesterol supplementation may benefit behaviour and general health. Trials are underway evaluating the use of statins to block the build-up of precursors.

## 13.3 Congenital disorders of glycosylation

Most extracellular proteins, membrane proteins and some intracellular proteins have glycans (oligosaccharide antenna-like structures) attached to them. This group of disorders results from defects in the synthesis of these carbohydrate moieties of glycoproteins. *N*-Glycans are linked to the amide group of asparagines and *O*-glycans are linked to the hydroxyl group of serine or threonine.

## *N*-Glycosylation defects

- Group I defects in the assembly of oligosaccharide chain synthesis and transfer to the protein
- Group II defects in the further processing of the protein-bound oligosaccharide chain.

The two most common disorders are congenital disorder of glycosylation (CDG) Ia (phosphomannomutase deficiency) and CDG Ib (phosphomannose isomerase deficiency).

CDGs are multiorgan disorders affecting particularly the brain, except CDG Ib which is mainly a hepatogastrointestinal disorder. CDG Ia has typical dysmorphology.

## Clinical features of CDG Ia

- Dysmorphic features – inverted nipples, fat pads
- Muscular hypotonia
- Faltering growth

- Cerebellar hypoplasia

## Diagnosis

Transferrin isoelectric focusing is used to screen for CDGs, but does not detect all of them. Enzymology is performed on white cells and fibroblasts.

## Management

CDG Ib is effectively managed with mannose supplementation. The other types are treated symptomatically.

### 13.4 Lesch–Nyhan syndrome

This is an X-linked disorder of purine metabolism caused by hypoxanthine–guanine phosphoribosyl-transferase (HGPRT) deficiency.

#### Clinical features of Lesch–Nyhan syndrome

- Motor disorder:
  - Hypotonia initially, evolving dystonia or choreoathetosis + spasticity
  - Bulbar disorder – speech and feeding difficulties
- Growth faltering
- Hyperuricaemia – stones, nephropathy, gout
- Compulsive self-injury
- Cognitive impairment

## Diagnosis

Elevated urate and hypoxanthine in urine. Plasma urate may be normal because of the excellent renal clearance in childhood and so a urinary urate must also be measured. Enzymology of red cells or fibroblast studies.

## Management

Allopurinol and liberal fluids are used to reduce the risk of renal complications. Urinary xanthine and urate should be assessed to ensure that the xanthine concentration remains below the limit of solubility, and may require reduction in allopurinol dose because xanthine stones are much less soluble than urate stones. Seating and positioning are essential to aid development and avoid self-injury together with relaxation techniques and communication skills. A full multidisciplinary team is essential. A low-purine diet is often undertaken but the evidence base for its use is limited.

## 13.5 Menkes syndrome

An X-linked membrane copper-transporter defect. Copper uptake by cells is normal; however, export from the cell is blocked and the copper-requiring enzymes do not receive the necessary copper for normal function.

### Clinical features of Menkes syndrome

- Hypothermia
- Epilepsy
- Hypotonia
- Prominent cheeks
- Pili torti
- Retardation
- Connective tissue problems
- Early death

### Diagnosis

Low serum copper and ceruloplasmin, although these may be normal in the neonatal period. Confirmed on copper-flux studies in fibroblasts, and ultimately by genotyping.

### Management

Daily copper–histidine injections have proven effective in altering the neurological outcome if the diagnosis is made early and treatment is not delayed. The connective tissue complications subsequently dominate the clinical picture in treated patients.

## 13.6 Ketotic hypoglycaemia

Ketotic hypoglycaemia (KH) is a common disorder presenting usually in late infancy, which usually resolves by 7–10 years of age. The underlying defect is unknown and likely to represent more than one metabolic defect. There is no specific diagnostic marker and it is usually a diagnosis of exclusion. KH classically presents in the morning after a prolonged fast and usually together with an intercurrent infection. At the time of hypoglycaemia, ketosis is marked. Alanine on amino acid analysis may be low. Management is the avoidance of fasting and using an emergency regimen (glucose polymer drinks) when unwell. If these drinks are not tolerated – refused, vomiting or diarrhoea – admission for intravenous 10% dextrose with appropriate electrolyte additives is required until fully feeding again.

## 14. SCREENING

## 14.1 Principles of screening

Screening for defined disorders aims to prevent avoidable morbidity and mortality. The sensitivity of a screening test is the rate of true positives, and its specificity is the rate of true negatives. The aim is not to miss any cases with the minimum of false positives. The necessary requirements for including a condition in a screening programme are as follows:

- Important health problem
- Accepted treatment
- Facilities available for diagnosis and treatment
- Latent or asymptomatic disease
- Suitable test
- Natural history understood
- Agreed case definition
- Early treatment improves prognosis
- Economic
- Case finding may need to be continuous

The UK National Screening Committee added a further requirement: randomized controlled trial evidence to support introduction of new screens.

## 14.2 UK neonatal screening programme

Neonatal blood spots are collected on day 6 with the aim of commencing treatment by day 21 for hypothyroidism and PKU. Laboratories still using the Guthrie test for PKU, which relies on phenylalanine-dependent bacterial growth, may give false negatives if the baby is receiving antibiotics. This information is requested on the card in those regions. The feeding status is also requested to ensure adequate protein intake, but newer techniques are able to detect PKU reliably on day 1 (routine screening day in the USA).

### Current UK programme

- Universal:
  - Congenital hypothyroidism (thyroid-stimulating hormone)
  - Phenylketonuria (phenylalanine)
  - Haemoglobinopathies (sickle cell disease and thalassaemia)
  - MCADD
  - Cystic fibrosis
- Some regions:
  - Galactosaemia
  - Homocystinuria
  - Duchenne muscular dystrophy

Duchenne muscular dystrophy is an example of a condition not fulfilling the criteria (being ultimately



incurable); however, the public and professional support for the programme has grown with time. An ‘important health problem’ has been interpreted on an individual rather than a population basis. Potential benefits include ‘avoidance of the diagnostic odyssey’, with all its associated emotional and financial expense before the correct diagnosis is made, influences on reproductive choice in the parents (at a time before subsequent pregnancies), and the hope that earlier identification may lead to positive interventions to influence outcome and better research.

Newer screening technologies, such as tandem mass spectrometry, further challenge the established criteria because it is now much easier to diagnose a whole number of not only inborn errors of metabolism, but also liver disease, haemoglobinopathies, etc. Although additional screening costs may be minimal because the current system of blood-spot collection can be utilized, there is a large burden placed on diagnostic and support services dealing with the new caseload. Rarity may no longer preclude screening a whole population when there is an effective treatment available, e.g. biotinidase deficiency cured with biotin supplementation.

The number of conditions screened for has massively increased in some countries. The USA screens for some 30 conditions; however, for many of these disorders the natural history is poorly understood and the diagnostic test does not always clearly decide who will develop symptoms. Concerns remain that individuals will be given a diagnostic label on the basis of a raised marker or mutation, but will never develop symptoms – the so-called ‘un-patient’. Considering MCAD deficiency screening, many new mutations have been detected since the introduction of screening, many of which have never previously been found in clinically presenting cases.

## 15. FURTHER READING

Campbell NP, Smith AD, Peters TJ (2005). *Biochemistry Illustrated*, 5th edn. London: Churchill Livingstone.

Hoffmann GF, Zschocke J, Nyhan WL, eds (2010). *Inherited Metabolic Diseases: A clinical approach*. Heidelberg: Springer.

Lyon G, Kolodny E, Pastores G (2006). *Neurology of Hereditary Metabolic Disease of Children*, 3rd edn. New York: McGraw Hill

McIntosh N, Helms P, Smyth R, Logan S, eds (2008). Inborn errors of metabolism: biochemical genetics. In: *Forfar and Arneil’s Textbook of Pediatrics*, 7th edn. London: Churchill Livingstone, Chapter 26.

Saudubray J-M, van den Berghe G, Walter J, eds (2011). *Inborn Metabolic Diseases: Diagnosis and treatment*, 5th edn. Berlin: Springer-Verlag.

## **CONTENTS**

### **1. Embryology, obstetrics and fetal medicine**

- [1.1 Embryology of the cardiovascular system](#)
- [1.2 Embryology and post-natal development of the respiratory system](#)
- [1.3 Embryology of the gastrointestinal system](#)
- [1.4 Embryology of the central nervous system](#)
- [1.5 Embryology of the genitourinary system](#)
- [1.6 Maternal conditions affecting the fetus and newborn](#)
- [1.7 Placental physiology, fetal growth and wellbeing](#)
- [1.8 Amniotic fluid, oligohydramnios and polyhydramnios](#)
- [1.9 Body composition at birth](#)
- [1.10 Hydrops fetalis](#)
- [1.11 Fetal circulation, adaptation at birth and persistent pulmonary hypertension of the newborn](#)

### **2. Prematurity – definitions and statistics**

- [2.1 Mortality – definitions](#)
- [2.2 Incidence and causes/associations of pre-term birth](#)
- [2.3 Outcome after pre-term birth](#)
- [2.4 Small-for-gestational-age babies](#)

### **3. Respiratory problems**

- [3.1 Surfactant deficiency](#)
- [3.2 Chronic lung disease \(bronchopulmonary dysplasia\)](#)
- [3.3 Meconium aspiration syndrome](#)
- [3.4 Pneumonia](#)
- [3.5 Pulmonary air leak](#)
- [3.6 Congenital lung problems](#)
- [3.7 Chest wall abnormalities](#)

[3.8 Upper airway obstruction](#)

[3.9 Principles of mechanical ventilation in neonates](#)

[3.10 Extracorporeal membrane oxygenation](#)

## **[4. Cardiovascular problems](#)**

[4.1 Patent ductus arteriosus](#)

[4.2 Hypotension](#)

[4.3 Hypertension](#)

[4.4 Cyanosis in the newborn](#)

## **[5. Gastroenterology and nutrition](#)**

[5.1 Necrotizing enterocolitis](#)

[5.2 Composition of infant milks](#)

[5.3 Breast-feeding](#)

[5.4 Fluid and nutritional requirements in neonates](#)

[5.5 Parenteral nutrition](#)

[5.6 Congenital abnormalities of the gastrointestinal system](#)

## **[6. Neurological problems](#)**

[6.1 Peri-intraventricular haemorrhage](#)

[6.2 Periventricular leukomalacia](#)

[6.3 Neonatal encephalopathy](#)

[6.4 Neonatal seizures](#)

[6.5 Causes of hypotonia in the newborn](#)

[6.6 Retinopathy of prematurity](#)

## **[7. Genitourinary problems](#)**

[7.1 Congenital abnormalities of the kidneys and urinary tract](#)

[7.2 Haematuria in the newborn](#)

[7.3 Causes of acute renal failure in neonates](#)

[7.4 Ambiguous genitalia](#)

## **[8. Infection](#)**

[8.1 Bacterial infection](#)

[8.2 Congenital viral infection](#)

[8.3 Fungal and protozoal infections](#)

## **[9. Neonatal endocrine problems](#)**

[9.1 Neonatal hypoglycaemia](#)

[9.2 Panhypopituitarism](#)

[9.3 Adrenal insufficiency](#)

## **[10. Neonatal jaundice](#)**

[10.1 Physiological jaundice](#)

[10.2 Causes of non-physiological jaundice](#)

[10.3 Management of non-physiological unconjugated hyperbilirubinaemia](#)

[10.4 Prolonged jaundice](#)

## **[11. Neonatal haematology/coagulation problems](#)**

[11.1 Polycythaemia](#)

[11.2 Haemorrhagic disease of the newborn and vitamin K](#)

[11.3 Disseminated intravascular coagulation](#)

[11.4 Haemophilia A](#)

[11.5 Von Willebrand disease](#)

## **[12. Neonatal orthopaedic problems](#)**

## **[13. Further reading](#)**

---

# Neonatology

---

## 1. EMBRYOLOGY, OBSTETRICS AND FETAL MEDICINE

### 1.1 Embryology of the cardiovascular system

- The heart develops initially as a tube from yolk sac mesoderm. It begins to beat from about 3 weeks' gestation
- In the fourth week the primitive heart loops to form four chambers. Septation between the four chambers and the aorta and pulmonary trunk occurs in the fifth week. The septum primum grows down from the upper part of the primitive atrium and then fuses with the endocardial cushions (septum intermedium) in the atrioventricular canal
- Bulbotruncal septation divides the common arterial trunk into the aorta and pulmonary trunk as spiral ridges develop in the caudal end of the heart. Completion of ventricular septation occurs as these fuse with the septum intermedium
- Blood is pumped caudally from the embryonic heart by six pairs of pharyngeal arch arteries to the paired dorsal aortas. Some of this system regresses and the third arch arteries form the carotid vessels. The right fourth arch artery forms the right subclavian artery with that of the left, forming the aortic arch. The left sixth arch artery forms the ductus arteriosus with branch pulmonary arteries forming from the right

### 1.2 Embryology and postnatal development of the respiratory system

- Embryonic phase (3–5 weeks' gestation) – the lung bud begins as an endodermal outgrowth of foregut. This branches into the surrounding mesoderm to form the main bronchi
- Pseudoglandular phase (6–16 weeks) – airways branch further to terminal bronchioles (preacinar airways). Cartilage, lymphatics and cilia form. Main pulmonary artery forms from sixth left branchial arch
- Canalicular phase (17–24 weeks) – airways lengthen, epithelium becomes cuboidal, pulmonary circulation develops. The acinar structures (gas-exchanging units) begin to develop and surfactant production begins by 24 weeks' gestation as type 1 and 2 pneumocytes become distinguishable. Lungs fill with amniotic fluid, which facilitates further lung growth
- Terminal sac phase (24–40 weeks) – further development of the acinar structures (respiratory bronchioles, alveolar ducts and terminal sacs [alveoli]) occurs and an increasing amount of

surfactant is produced. Type 1 pneumocytes eventually cover approximately 95% of the alveolar surface and facilitate gas exchange. The surfactant-producing type 2 cells cover only about 5%. Development of the pulmonary circulation continues and results in a thicker intra-arteriolar smooth muscle layer by term, which may respond to intrauterine hypoxia by vasoconstriction. This regresses rapidly after birth

- Postnatal lung development – the number and size of alveoli increase rapidly during the first 2 years (approximately 150 million at term to 400 million by 4 years). The conducting airways also increase in size
- Diaphragm development – arises as a sheet of mesodermal tissue, the septum transversum. It begins close to the third, fourth and fifth cervical segments and therefore its nerve supply, the phrenic nerve, is derived from this area. The primitive septum transversum migrates caudally to form the pleural space and the two posterolateral canals in which the lung buds develop fuse. Failure to do this results in a Bochdalek hernia. Failure of the retrosternal part of the septum transversum to form causes a Morgagni-type diaphragmatic hernia. The diaphragm is completed as primitive muscle cells migrate from the body wall. If this fails, eventration of the diaphragm results

### 1.3 Embryology of the gastrointestinal system

- The endodermal lining of the yolk sac forms the primitive gut
- The midgut lengthens and protrudes into the yolk sac via the vitelline duct. Meckel's diverticulum is the remnant of this
- The extra-abdominal gut rotates 270° anticlockwise around the mesentery which contains the superior mesenteric artery. Failure to complete this results in malrotation
- The gut returns to the abdominal cavity by the end of week 12. Exomphalos is the result of this not occurring
- Gastroschisis is a failure of closure of the anterior abdominal wall

### 1.4 Embryology of the central nervous system

- The neural plate develops from ectoderm and forms the neural tube by 3 weeks' gestation. The neural groove closes in a cranial-to-caudal direction by the end of the fourth week
- Three swellings evolve from the caudal end of the neural tube – the prosencephalon (forebrain) forms the cerebral hemispheres, the mesencephalon forms the midbrain, and the rhombencephalon (hind brain) forms the pons, medulla and cerebellum
- Neuroblasts migrate from the centre of the brain to further develop the cerebral hemispheres
- Myelination from Schwann cells occurs from 12 weeks' gestation. Myelination accelerates from about 24 weeks but is not complete until around 2 years of age. This has important implications for the interpretation of brain MR (magnetic resonance) scans in neonates and early childhood
- Neural crest cells form the meninges, peripheral nerves, chromaffin cells, melanocytes and adrenal medulla

## 1.5 Embryology of the genitourinary system

- The genitourinary systems develop from mesoderm on the posterior abdominal wall and drain into the urogenital sinus of the cloaca
- The pronephros is the primitive kidney resulting from this and is replaced initially by the mesonephros. The ureteric bud appears at the start of week 5 of embryogenesis as a small branch of the mesonephric duct. The mesonephric (wolffian) ducts drain urine from primitive tubules into the urogenital sinus. Repeated branching from week 6 onwards gives rise to the calyces, papillary ducts and collecting tubules by week 12
- Differentiation of the metanephros into nephrons – glomeruli, tubules and loop of Henle occurs from 4 weeks. These structures then join with the lower wolffian ducts to form the collecting systems. Branching and new nephron induction continues until week 36
- The metanephros develops from the most caudal part of the mesodermal ridge, but the kidney eventually becomes extrapelvic because of the growth of surrounding areas
- The Y chromosome (*SRY* gene) influences development of primitive gonads to form testes after 6 weeks. Testes 'secrete' müllerian inhibition factor (MIF) which results in regression of müllerian structures (uterus, fallopian tubes and vagina)
- Testosterone influences the development of wolffian structures (prostate, seminiferous tubules and vas deferens) as well as later masculinization

## 1.6 Maternal conditions affecting the fetus and newborn

- **Diabetes:**
  - Threefold increased risk of congenital malformations (congenital heart disease, sacral agenesis, microcolon, neural tube defects)
  - Small for gestational age (SGA) three times the normal rate because of small-vessel disease
  - Macrosomia as a result of increased fetal insulin
  - Hypoglycaemia
  - Hypocalcaemia
  - Hypomagnesaemia
  - Surfactant deficiency
  - Transient hypertrophic cardiomyopathy (septal)
  - Polycythaemia and jaundice
- **Hypertension and pre-eclampsia** – SGA, polycythaemia, neutropenia, thrombocytopenia, hypoglycaemia
- **Maternal thyroid disease**
  - Neonatal thyrotoxicosis can be caused by transplacental thyroid-stimulating antibodies (i.e. long-acting thyroid stimulator [LATS]) with maternal Graves disease
  - Rare – only 1:70 mothers with thyrotoxicosis
  - May present with fetal tachycardia or within 1–2 days of birth, but sometimes delayed if mother is taking antithyroid drugs
  - Usually causes goitre
  - Thyroid function tests (TFTs) should be assessed between 7 and 10 days in all babies of mothers

with Graves disease (or sooner if the baby is symptomatic)

- Only severe cases require treatment with  $\beta$  blockers and antithyroid drugs because it resolves spontaneously as antibody levels fall over the first few months

Neonatal hypothyroidism may be caused by maternal antithyroid drugs taken during pregnancy, so check TFTs between 4 and 7 days after birth.

## **Systemic lupus erythematosus**

Maternal systemic lupus erythematosus (SLE) is associated with:

- Increased risk of miscarriage; recurrent miscarriage is associated with antiphospholipid antibody
- Increased risk of SGA babies. Risk is higher with maternal hypertension and renal disease
- Congenital complete heart block – associated with presence of anti-Ro and anti-La antibodies
- Butterfly rash – transient because of transplacental passage of SLE antibodies

## **Thrombocytopenia**

Transplacental passage of maternal antiplatelet antibodies causes neonatal thrombocytopenia. If the mother is also thrombocytopenic, the cause is likely to be maternal idiopathic thrombocytopenia (also associated with maternal SLE):

- Platelet count proportional to that of mother
- Rarely causes very low neonatal platelet counts or symptoms
- Risk of intracranial haemorrhage if platelet count  $<50 \times 10^9/l$  (may occur antenatally, so caesarean section not always protective)
- Treatment: intravenous immunoglobulin G (IgG) and platelet transfusion

Alloimmune thrombocytopenia occurs following maternal sensitization if mother is PL<sup>A1</sup> antigen negative:

- Approximately 3% of white people are PL<sup>A1</sup> antigen negative
- First pregnancies may be affected; severity is usually greater in subsequent pregnancies
- Antenatal intracranial haemorrhage is common (20–50%)
- Treatment – washed irradiated maternal platelets or intravenous IgG and random donor platelets

## **Myasthenia gravis**

Babies of mothers with myasthenia gravis have a 10% risk of a transient neonatal form of the disease:

- Usually the result of transplacental passage of anti-acetylcholinesterase receptor antibodies but baby may produce own antibodies
- Risk is increased if a previous baby was affected
- Maternal disease severity does not correlate with that of baby; a range of symptoms from mild hypotonia to ventilator-dependent respiratory failure may occur



- Diagnosis – antibody assay, electromyography and edrophonium or neostigmine test (also used as treatment)
- Babies of mothers with myasthenia gravis should be monitored for several days after birth
- Usually presents soon after birth and resolves by 2 months. Physiotherapy may be required to prevent/relieve contractures
- Congenital myasthenia gravis should be considered if antibodies are absent or if symptoms persist or recur

## **Fetal alcohol syndrome**

Although more than three or four alcohol units per day during pregnancy are thought to be necessary to cause fetal alcohol syndrome, even moderate alcohol intake may reduce birthweight.

Features of fetal alcohol syndrome include:

- Small for gestational age
- Dysmorphic face with mid-face hypoplasia – short palpebral fissures, epicanthic folds, flat nasal bridge (resulting in small upturned nose), long philtrum, thin upper lip, micrognathia and ear abnormalities
- Microcephaly with subsequent intellectual impairment
- Congenital heart disease
- Postnatal growth failure

## **Maternal smoking**

- Reduces birth weight by 10% on average
- Increases risk of sudden infant death syndrome

## **Maternal drugs**

Teratogenic drugs include:

- Phenytoin (fetal hydantoin syndrome) – dysmorphic face (broad nasal bridge, hypertelorism, ptosis, ear abnormalities)
- Valproate – neural tube defects, fused metopic suture, mid-face hypoplasia, congenital heart disease, hypospadias, talipes, global developmental delay
- Retinoids (isotretinoin) and large doses of vitamin A – dysmorphic face (including cleft palate), hydrocephalus, congenital heart disease
- Cocaine – SGA, prune belly and renal tract abnormalities, gut, cardiac, skeletal and eye malformations
- Other teratogenic drugs include thalidomide (limb defects), lithium, carbamazepine, chloramphenicol and warfarin

## **Maternal opiate abuse**

- Associated with intrauterine growth retardation (IUGR)
- Results in withdrawal symptoms or neonatal abstinence syndrome – onset usually within 1–2 days of birth but may be delayed until 7–10 days and continue for several months; onset is later and symptoms persist for longer with methadone

Symptoms are:

- **Wakefulness**
- **Irritability**
- **Tremors**, temperature instability, tachypnoea
- **High-pitched cry**, hyperactivity, hypertonia
- **Diarrhoea**, disorganized suck
- **Respiratory distress**, rhinorrhoea
- **Apnoea**
- **Weight loss**
- **Autonomic dysfunction**
- **Lacrimation**

Also seizures, myoclonic jerks, hiccups, sneezing, yawning

- Surfactant deficiency is less common
- Sudden infant death syndrome is more common
- Management – monitor using withdrawal score chart. Less than 50% require pharmacological intervention. Indications for this are severe withdrawal symptoms or seizures. Oral morphine is the usual treatment of choice. Methadone, phenobarbital, benzodiazepines and chlorpromazine have also been used

## 1.7 Placental physiology, fetal growth and wellbeing

The fertilized ovum divides to form a blastocyst which attaches itself to the inside wall of the uterus. The outer cells of the blastocyst, the trophoblasts, eat their way into the endometrium and these and surrounding endometrial cells form the placenta and membranes. The trophoblasts are therefore the source of nutrition for the early embryo in the first 12 weeks.

In the second and third trimesters, maternal blood flows into the placental sinuses which surround the placental villi. Active transport of amino acids and other nutrients occurs across the chorionic epithelium into the villi, early in pregnancy, but this becomes less after the first trimester. Oxygen and nutrients diffuse into the fetal blood supply via the villi. Diffusion of oxygen occurs because maternal  $PO_2$  is approximately 7 kPa, compared with 4 kPa in the fetus.

## Oestrogen

- Initially produced by the corpus luteum and then in increasing amounts by the placenta as pregnancy

progresses

- Causes the uterine smooth muscle to proliferate
- Enhances development of the uterine blood supply
- Changes pelvic musculature and ligaments to facilitate birth
- Causes breast development by increasing proliferation of glandular and fatty tissue

## **Progesterone**

- Limited amounts produced by the corpus luteum in the early part of pregnancy – much larger amounts produced by the placenta after the first trimester
- Causes endometrial cells to store nutrients in first trimester
- Relaxes uterine smooth muscle; decrease in secretion of progesterone in the final few weeks of pregnancy coincides with onset of labour
- Facilitates glandular development of breasts

## **Human chorionic gonadotrophin**

- Secreted by trophoblasts
- Prevents degeneration of corpus luteum
- Peak concentration at around 10 weeks; falls rapidly to low levels by 20 weeks' gestation

## **Human placental lactogen**

- Secreted by placenta in increasing amounts throughout pregnancy
- Has growth hormone-like effect on fetus
- Has prolactin-like effect on breasts, facilitating milk production

## **Oxytocin**

- Produced by the hypothalamic–posterior pituitary axis
- Release is stimulated by irritation of the cervix
- Oxytocin causes contraction of uterine smooth muscle
- Causes milk secretion – stimulation via the hypothalamus

## **Prolactin**

- Produced by the hypothalamic–anterior pituitary axis
- Production is inhibited during pregnancy by high levels of oestrogen and progesterone produced by the placenta; the sudden decrease in these after delivery of the placenta increases prolactin release
- Prolactin causes secretion of milk from the breasts
- Hypothalamic production of a prolactin inhibitory factor increases if the breasts are engorged with milk and decreases as the baby breast-feeds
- Prolactin inhibits follicle-stimulating hormone immediately postpartum, thereby preventing ovulation

## Identifying fetal compromise

- Kick charts
- Symphysis–fundus height – to estimate fetal size/growth
- Ultrasound scan measurement – to estimate fetal size/growth
- Amniotic fluid volume (see below)
- Umbilical artery Doppler studies – reflect placental blood flow
- Fetal Doppler scans – reflect hypoxia if abnormal
- Biophysical profile – fetal movement, posture and tone, breathing, amniotic fluid volume and cardiotachograph assessed

## 1.8 Amniotic fluid, oligohydramnios and polyhydramnios

- Amniotic fluid is produced by the amnion, fetal urine and fetal lung secretions
- Oligo- or polyhydramnios is diagnosed on ultrasound scan if clinically suspected
- Deepest pool of amniotic fluid normally 3–8 cm. The amniotic fluid index (AFI) is the sum of the depth of the deepest pool in each quadrant
- Oligohydramnios (decreased AFI) may be caused by:
  - Placental insufficiency (IUGR is usually also present)
  - Fetal urinary tract abnormalities
  - Prolonged rupture of membranes (PROM)
- Polyhydramnios (increased AFI) may be the result of:
  - Maternal diabetes
  - Karyotype abnormalities
  - Twin-to-twin transfusion syndrome (sometimes called polyhydramnios–oligohydramnios sequence)
  - Neuromuscular disorders such as:
    - Congenital myotonic dystrophy
    - Spinal muscular atrophy (types 1 or 0 – type 0 is antenatal presentation of the disease)
    - Congenital myopathies
    - Möbius syndrome
- Oesophageal atresia
- Congenital diaphragmatic hernia
- Idiopathic/unexplained (a cause is more likely to be found in severe cases)

## 1.9 Body composition at birth

- There is a gradual decrease in extracellular fluid with increasing gestation (approximately 65% of weight at 26 weeks, 40% at 40 weeks)
- Early postnatal diuresis occurs within 1–2 days because of further loss of extracellular (interstitial) fluid and partly accounts for up to 10% of the weight loss – this may be delayed in babies with respiratory failure

- Surface area to weight ratio is high in newborn babies (more so in preterm infant) so that the heat loss to heat production ratio is also high
- Newborn babies are able to generate heat as a response to cold stress using brown adipose tissue (non-shivering thermogenesis). Peripheral vasoconstriction may also help maintain body temperature. These mechanisms may be impaired in preterm or sick babies and are also limited during the first few hours of postnatal life

## 1.10 Hydrops fetalis

Definition: subcutaneous oedema and fluid in at least two of: pleural effusions, ascites, pericardial effusion.

### Causes

**Immune** cause is usually rhesus disease.

**Non-immune** causes include:

- Anaemia:
  - Twin-to-twin transfusion
  - Fetomaternal haemorrhage
  - Homozygous  $\alpha$ -thalassaemia
- Heart failure:
  - Arrhythmias (supraventricular tachycardia, complete heart block)
  - Structural (cardiomyopathy, hypoplastic left and right heart, etc.)
  - High output (arteriovenous malformations, angiomas)
- Chromosomal abnormalities (Turner syndrome, trisomy 21 and other trisomies)
- Congenital malformations:
  - Congenital cystic adenomatoid malformation
  - Diaphragmatic hernia
  - Cystic hygroma
  - Chylothorax and pulmonary lymphangiectasia
  - Osteogenesis imperfecta
  - Asphyxiating thoracic dystrophy
- Infection:
  - Parvovirus B19
  - Cytomegalovirus (CMV)
  - Toxoplasmosis
  - Syphilis
  - Chagas disease (a South American parasite infection)
- Congenital nephrotic syndrome
- Idiopathic – 15–20% cases

## 1.11 Fetal circulation, adaptation at birth and persistent pulmonary hypertension of the newborn

### Fetal haemoglobin (HbF)

- Four globin chains are  $\alpha_2\gamma_2$  (adult is predominantly  $\alpha_2\beta_2$ )
- The  $\gamma$  chains have reduced binding to 2,3-diphosphoglycerate (2,3-DPG)
- The reduced 2,3-DPG in HbF causes the oxyhaemoglobin dissociation curve to be shifted to the left, i.e. there is a higher saturation for a given  $PO_2$  or  $P_{50}$  decreases (the  $PO_2$ ) at which half the haemoglobin is saturated. Fetal red blood cells therefore have a higher affinity for oxygen, making it easier to unload from the maternal circulation. Delivery of oxygen to the fetal tissues is facilitated by the steep oxyhaemoglobin dissociation curve of HbF, but the lower  $P_{50}$  leads to a decreased rate of unloading to tissues. Levels of 2,3-DPG rise rapidly in the first few days to meet the increased metabolic requirements that occur after birth. Preterm infants have lower 2,3-DPG levels and therefore have a limited ability for oxygen to be unloaded from red blood cells
- Approximately 80% of haemoglobin is HbF at term. This falls to <10% by 1 year
- The following also shift the oxyhaemoglobin dissociation curve to the left:
  - Alkalosis
  - Hypocapnia
  - Hypothermia

### Circulatory changes at birth

- Functional closure of the ductus venosus occurs within hours of birth, with anatomical closure completed within 3 weeks
- Ductus arteriosus patency is maintained in fetal life by prostaglandin  $E_2$  and prostaglandin  $I_2$  (prostacyclin). Functional closure of the ductus arteriosus usually occurs within 15 hours of birth and is facilitated by:
  - Reduced sensitivity of the ductus to prostaglandins and increased breakdown of prostaglandin  $E_2$  occurring in the lungs towards the end of pregnancy
  - Increased  $PO_2$  after the onset of breathing
  - Reduced pulmonary vascular resistance
- Before birth only about 10% of cardiac output goes to the lungs because pulmonary vascular resistance is higher than systemic vascular resistance
- Chemosensitivity of the pulmonary arteriolar bed increases with advancing gestation
- Increased  $PO_2$  and lung expansion immediately after birth, along with increased release of vasodilator substances (prostaglandins, bradykinin and nitric oxide), lead to a fall in pulmonary vascular resistance after birth
- Pulmonary artery pressure falls to half the prebirth levels within 24 hours and pulmonary blood flow doubles as a result
- After birth, the left atrial pressure increases as a result of increased pulmonary blood flow and right atrial pressure falls because of the absence of placental blood from the umbilical vein. This

causes a functional closure of the foramen ovale within a few minutes of birth. Anatomical closure may take weeks

## Persistent pulmonary hypertension of the newborn

- Normal circulatory changes after birth are delayed either because of increased muscularization of the pulmonary arterioles or as a response to hypoxia
- Treatment includes ventilation with hyperoxia, induced metabolic alkalosis and the use of pulmonary vasodilators such as nitric oxide

## Nitric oxide

- Free radical
- Synthesized in endothelial cells from L-arginine by the enzyme nitric oxide synthase – also known as endothelium-derived relaxing factor
- In vascular smooth muscle – nitric oxide activates guanylyl cyclase to increase intracellular guanosine cyclic 3':5'-monophosphate (cGMP). This leads to smooth muscle relaxation and vasodilatation by stimulating cGMP-dependent protein kinase which reduces intracellular calcium

## 2. PREMATURITY – DEFINITIONS AND STATISTICS

### 2.1 Mortality – definitions

- **Stillbirth** – *in utero* death after 24 weeks' gestation (28 weeks in most other European countries, 20 weeks in USA, 12 weeks in Japan). Stillbirth rate for England, Wales and Northern Ireland in 2009 = 4.7 per 1000 live- and stillbirths
- **Perinatal mortality rate** – stillbirths and deaths within 6 days of birth per 1000 live- and stillbirths. Perinatal mortality rate for England, Wales and Northern Ireland in 2009 = 6.8
- **Neonatal mortality rate** – deaths of liveborn infants < 28 days old per 1000 live births. Neonatal mortality rate for England, Wales and Northern Ireland in 2009 = 2.8. Note that perinatal and neonatal mortality rates are adjusted by removing terminations of pregnancy and babies born <22 weeks' gestation

### 2.2 Incidence and causes/associations of preterm birth

Approximate UK incidences (live births) are:

- |   |      |
|---|------|
| • Preterm birth (i.e. before 37 completed weeks' gestation) | 7%   |
| • Low birthweight (<2500 g)                                 | 7%   |
| • Very low birthweight (<1500 g)                            | 1.2% |
| • Extremely low birthweight (<1000 g)                       | 0.5% |

All of these incidences are higher in developing countries but lower in some other European countries.

The incidence of preterm birth appears to be increasing both in the UK and in other countries, and this is probably the result of:

- Increased number of multiple births because of assisted conception
- Increased obstetric intervention
- Increased use of gestational age assessments (which tends to decrease estimates of gestational age)
- An increase in the registration of live births at very low gestation

The following are associated with an increased risk for spontaneous preterm birth:

- Social/demographic factors:
  - Maternal country of birth Africa or Caribbean
  - Low socioeconomic class
  - Age <20 or >40 years
- Past obstetric or medical history:
  - Previous preterm birth
  - Uterine abnormalities
  - Cervical abnormalities
- Current pregnancy:
  - Multiple pregnancy
  - Poor nutrition
  - Low pre-pregnancy weight
  - Poor pre- and antenatal care
  - Anaemia
  - Smoking
  - Bacteriuria
  - Genital tract colonization (particularly group B streptococci)
  - Cervical dilatation >1 cm
  - Pre-term PROM

## 2.3 Outcome after pre-term birth

The first national study of survival and long-term follow-up after extreme preterm birth to be published was the EPICure study. This documented outcome after birth between 20 and 25 weeks' gestation in 1289 live births in the UK and Republic of Ireland in 1995. The study was repeated in 2006, for England only, and also included babies of 26 weeks' gestation.

Survival to discharge from hospital was as follows:

1995	2006
------	------



- 22 weeks 1% 5%
- 23 weeks 11% 16%
- 24 weeks 26% 42%
- 25 weeks 44% 65%
- 26 weeks — 75%

Neurodevelopmental follow-up of survivors from the 1995 birth cohort at 30 months showed:

- No disability 49%
- Severe disability 24%
- Mild-to-moderate disability 24%
- Died after hospital discharge 2%
- Not followed up 1%

Outcome for preterm SGA infants is less well documented but there is some evidence that outcome is marginally better than that expected in an appropriately grown infant of the same birthweight, i.e. a baby born at 28 weeks weighing 750 g (below the third centile) would be expected to have the same outcome as a 25 weeks' gestation infant of the same weight (50th centile).

The ethics of resuscitation of extremely preterm infants are controversial and any decisions in individual cases should be made by the most senior paediatrician available at the time, with parents' views taken into consideration when possible. It seems reasonable to actively resuscitate most appropriately grown (i.e. more than approximately 500 g) infants greater than 23 weeks' gestation who have reasonable signs of life after birth.

## 2.4 Small-for-gestational-age babies

- The definition of SGA varies between birthweight <3rd centile and a birthweight <10th centile. Over 50% of babies with birthweight <10th centile are constitutionally small; the rest have IUGR
- There are many causes of SGA infants including maternal (hypertension, diabetes, lupus, smoking, altitude), placental and fetal (multiple gestations, malformations, infections)

## Fetal/neonatal complications of IUGR

- *In utero* death/stillbirth
- Fetal hypoxia/acidosis (associated with neonatal encephalopathy/birth depression)
- Polycythaemia, neutropenia (and increased infection risk), thrombocytopenia
- Hypothermia
- Hypoglycaemia
- Necrotizing enterocolitis

# Long-term complications of IUGR

- Increased risk of neurodevelopmental problems
- Hypertension
- Diabetes
- Hyperlipidaemias

## 3. RESPIRATORY PROBLEMS

### 3.1 Surfactant deficiency

Endogenous surfactant is produced by type 2 pneumocytes, which line 5–10% of the alveolar surface. Surfactant-containing osmiophilic granular inclusion bodies cause these to appear different from the thinner and more numerous type 1 pneumocytes, which are responsible for gas exchange.

### Composition of endogenous surfactant

#### Phospholipids – 80-85%

- The main surface-active components, which lower surface tension at the air–alveolar interface preventing alveolar collapse
- Dipalmitoylphosphatidylcholine (DPPC) – 45–70% – is the major constituent of all exogenous surfactant preparations
- Other phospholipids include:
  - Phosphatidylcholine
  - Phosphatidylglycerol
  - Phosphatidylinositol
  - Phosphatidylethanolamine
  - Phosphatidylserine

#### Other lipids – 10% (e.g. sphingomyelin)

#### *Surfactant proteins – 5–10%*

- Facilitate adsorption, spreading and recycling of surfactant and have immunoregulatory properties
- Surfactant protein A:
  - Mainly immune function but also has a role in spreading and recycling of surfactant
  - Has been shown to increase microbial killing by alveolar macrophages
  - Increases resistance to inhibitors of surface activity which occurs in sepsis
- Surfactant protein B:
  - Major role in adsorption, spreading and recycling of surfactant
  - Case reports suggest that congenital deficiency of surfactant protein B is a lethal, autosomal recessive condition
- Surfactant protein C:

- Similar function to surfactant protein B
- Surfactant protein D:
  - Immune function

**Platelet-activating factor (PAF)**

- May increase surfactant secretion

**Exogenous surfactants**

	Contains	Onset	Mortality	Air leak	CLD/BPD
Synthetic	DPPC Hexadecanol Tyloxapol	Hours	↓	↓	↓
Animal	Lipids (including DPPC) Surfactant proteins B + C	Minutes	↓↓	↓↓	↓↓

CLD/BPD, chronic lung disease/bronchopulmonary dysplasia; DPPC, dipalmitoylphosphatidylcholine.

**Estimated incidence of surfactant deficiency by gestational age (without maternal steroids)**

Gestation (completed weeks)	Incidence of surfactant deficiency (%)
26	90
27	85
28	80
29	75
30	70
31	60
32	55
33	40
34	25
35	20
36	12
37	6
38	3
39	2
40	<1–2

Increased incidence of surfactant deficiency in:

- Prematurity

- Male sex
- Sepsis
- Maternal diabetes
- Second twin
- Elective caesarean section
- Strong family history

Surfactant deficiency is decreased in:

- Female sex
- PROM
- Maternal opiate use
- IUGR
- Antenatal glucocorticoids
- Prophylactic surfactant

Amniotic fluid (or gastric aspirate) lecithin:sphingomyelin (L:S) ratios:

- $<1.5$  = immature – 70% risk of surfactant deficiency
- $1.5-1.9$  = borderline – 40% risk of surfactant deficiency
- $2.0-2.5$  = mature – very small risk unless mother has diabetes
- $>2.5$  = safe

## Management of surfactant deficiency

Maternal antenatal corticosteroids (betamethasone or dexamethasone) before preterm birth reduce the effects of surfactant deficiency and have been shown to:

- Reduce neonatal mortality by approximately 31%
- Decrease intraventricular haemorrhage by approximately 46%
- Reduce the risk of necrotizing enterocolitis (NEC)
- Decrease the need for respiratory support for respiratory distress syndrome (RDS)
- Decrease the need for neonatal intensive care unit (NICU) admission
- Reduce the risk of infection in the first 48 hours

The current Royal College of Obstetricians and Gynaecologists (RCOG) guidelines suggest giving maternal corticosteroids to women with likely pre-term birth between week 24 and  $34^{+6}$  of gestation, and also to consider in those from  $23^{+0}$  weeks, as well as before any elective caesarean section up to  $38^{+6}$  weeks.

There is currently no evidence that routine high-frequency oscillation is of any long-term benefit in preterm infants with surfactant deficiency, although this mode of ventilation may be used as a ‘rescue’ in severe cases.

Routine paralysis is not used in most neonatal units. Sedation with opiates and various modes of

trigger ventilation may help reduce the incidence of pneumothoraces.

Exogenous surfactant considerably reduces mortality and incidence of pneumothoraces and chronic lung disease. Early treatment with surfactant and use of animal rather than synthetic surfactants enhance these outcomes.

## 3.2 Chronic lung disease – bronchopulmonary dysplasia

Definition – respiratory support with supplementary oxygen  $\pm$  mechanical ventilation for >28 days with typical chest radiograph changes (see below). In very-low-birthweight (VLBW) infants an alternative definition has been suggested – requiring oxygen  $\pm$  mechanical ventilation >36 weeks corrected gestational age and typical changes on a chest radiograph.

### Risk factors for chronic lung disease

- Prematurity
- Prolonged mechanical ventilation with high pressures and high fractional inspired oxygen ( $FiO_2$ )
- Lung over-inflation (volutama or barotrauma) or under-inflation (‘atelectotrauma’)
- Oxygen toxicity (free radical mediated)
- Pulmonary air leak (pneumothoraces or pulmonary interstitial emphysema)
- Gastro-oesophageal reflux
- Patent ductus arteriosus (PDA)
- Chorioamnionitis
- Postnatal infection (particularly with *Ureaplasma urealyticum* and cytomegalovirus)

### Radiological stages

- Stage 1: first few days – indistinguishable from surfactant deficiency
- Stage 2: 2nd week – generalized opacity of lung fields
- Stage 3: 2–4 weeks – streaky infiltrates
- Stage 4: >4 weeks – hyperinflation, cysts, areas of collapse/consolidation, cardiomegaly

### Management of chronic lung disease

- Ventilatory support as required
- Randomized controlled trial (RCT) evidence suggests no benefit of a high oxygen saturation target (i.e. 95-98%) compared with a lower level (91–94%)
- Good nutrition is of paramount importance; increased alveolar growth accompanies general growth – particularly in the first 1–2 years
- Treatment of underlying exacerbating factors – infection, gastro-oesophageal reflux, fits, cardiac problems, etc.
- Dexamethasone – the only proven benefit is to facilitate weaning off mechanical ventilation but

concern has been raised over short-term side effects (hyperglycaemia, hypertension, bradycardia, poor growth, increased risk of sepsis) and long-term side effects (adverse neurodevelopmental outcome, particularly cerebral palsy)

- Inhaled steroids – only proven benefit is to reduce the need for systemic steroids
- Bronchodilators – used only if there is evidence of reversible airway obstruction
- Diuretics – likely to be of benefit only in the presence of PDA, cor pulmonale or excessive weight gain
- Respiratory syncytial virus (RSV) prophylaxis with monoclonal antibodies (e.g. palivizumab) has been shown to reduce hospitalization in high-risk cases, but use is controversial because of the high cost of the drug and the need for monthly intramuscular injections throughout the RSV season

## **Outcome of babies with chronic lung disease**

- Most are weaned off supplementary oxygen before discharge home
- Few require home oxygen
- Most babies discharged on home oxygen are weaned off before 1–2 years
- High risk of readmission to hospital with viral respiratory infections in the first 1–2 years of life
- Increased risk of recurrent cough and wheeze in pre-school age group but most outgrow this tendency and have normal exercise tolerance in childhood

## **3.3 Meconium aspiration syndrome (MAS)**

### **Risk factors**

- Term or post-term (incidence much higher in births after 42 weeks)
- Small for gestational age
- Perinatal asphyxia

Rare in preterm but said to occur with congenital listeriosis (more likely to be pus than meconium). The passage of meconium in fetal distress may be the result of increased secretion of motilin. Meconium may be inhaled antenatally or postnatally. Antenatal inhalation is more likely in fetal distress because of abnormal fetal breathing (equivalent to gasping) that occurs with hypoxia and acidosis.

### **Major effects of MAS on lung function**

- Airway blockage:
  - Increased airway resistance with ball–valve mechanism and gas trapping
  - High risk of pneumothorax
- Chemical pneumonitis
- Increased risk of infection:
  - Even though meconium is sterile
  - *Escherichia coli* is the most common infective agent

- Surfactant deficiency:
  - Lipid content of meconium displaces surfactant from alveolar surface
  - Persistent pulmonary hypertension of the newborn

MAS changes on chest radiographs include initial patchy infiltration and hyperinflation. Pneumothoraces are common at this stage. A more homogeneous opacification of the lung fields may develop over the next 48 hours, as chemical pneumonitis becomes more of a problem. In severe cases, changes similar to chronic lung disease may develop over the following weeks.

There is no evidence for routine suction if the baby is vigorous and otherwise in good condition. Intubation for lower airway suction is only needed if meconium can be seen below the vocal cords. Thoracic compression and routine bronchial lavage have no proven benefit. Intermittent positive-pressure ventilation with a relatively long expiratory time to prevent further gas trapping may be required in moderate-to-severe MAS. Surfactant replacement therapy in infants with MAS has proven benefit, but large doses may be required. Extracorporeal membrane oxygenation (ECMO) may be used in the most severe cases.

### 3.4 Pneumonia

Pneumonia can be congenital, intrapartum or nosocomial.

#### Congenital

Onset is usually within 6 hours of birth:

- **Bacterial:**
  - Streptococci (group B streptococci)
  - Coliforms (*E. coli*, *Klebsiella*, *Serratia*, *Shigella*, *Pseudomonas* spp., etc.)
  - Pneumococci
  - *Listeria* sp.
- **Viral**
  - CMV
  - Rubella virus
  - Herpes simplex virus
  - Coxsackievirus
- **Other**
  - Toxoplasmosis
  - *Chlamydia* sp.
  - *Ureaplasma urealyticum*
  - *Candida* sp.

#### Intrapartum

Onset is usually within 48 hours:

- **Bacterial:**
  - Group B streptococci
  - Coliforms (as above)
  - *Haemophilus* sp.
  - Staphylococci
  - Pneumococci
  - *Listeria* sp.
- **Viral:**
  - Herpes simplex virus
  - Varicella-zoster virus

## Nosocomial

Onset is after 48 hours:

- **Bacterial:**
  - Staphylococci
  - Streptococci
  - *Pseudomonas* sp.
  - *Klebsiella* sp.
  - Pertussis
- **Viral:**
  - RSV
  - Adenovirus
  - Influenza viruses
  - Parainfluenza viruses
  - Common cold viruses
- **Other:**
  - *Pneumocystis jiroveci*

## 3.5 Pulmonary air leak

### Pneumothorax

- Occurs in up to 1% of otherwise healthy term infants (it is usually asymptomatic)
- Overdistension of alveoli is more likely to occur in immature lungs because of a decreased number of pores of Kohn, which redistribute pressure between alveoli. Air ruptures through overdistended alveolar walls and moves towards the hilum where it enters the pleural or mediastinal space
- More common in surfactant deficiency, MAS, pneumonia and pulmonary hypoplasia
- Risk is reduced by volume target ventilation or lower ventilator pressures to avoid overdistension, faster rate ventilation with shorter inspiratory times, paralysis of infants fighting the ventilator and surfactant replacement therapy



## **Pulmonary interstitial emphysema**

- May occur in up to 25% of VLBW infants, usually confined to those with the worst surfactant deficiency
- May be more common in chorioamnionitis
- Alveolar rupture results in small cysts in the pulmonary interstitium
- Ventilation is difficult and mortality and incidence of chronic lung disease are high

## **Pneumomediastinum**

- May complicate surfactant deficiency or other forms of neonatal lung disease, when it may coexist with pneumothorax or may be iatrogenic following tracheal rupture secondary to intubation
- No symptoms may occur in isolated pneumomediastinum, but respiratory and cardiovascular compromise is more likely to occur if pneumothorax is also present

## **3.6 Congenital lung problems**

### **Pulmonary hypoplasia**

Primary pulmonary hypoplasia is rare but may present with persistent tachypnoea which resolves with lung growth several months after birth.

Secondary pulmonary hypoplasia may be the result of:

- Reduced amniotic fluid volume – Potter syndrome (renal agenesis) or other severe congenital renal abnormalities resulting in markedly decreased urine volume (infantile [autosomal recessive] polycystic kidney disease, severe bilateral renal dysplasia, posterior urethral valves)
- Preterm rupture of membranes – occurs only if membranes ruptured before 26 weeks; 23% of pregnancies with rupture of membranes before 20 weeks are unaffected; outcome with rupture of membranes before 24 weeks is usually poor
- Amniocentesis – mild-to-moderate respiratory symptoms are more likely to occur in the neonatal period and incidence of respiratory symptoms in the first year of life is increased
- Lung compression – pulmonary hypoplasia is common in small-chest syndromes including asphyxiating thoracic dystrophy and thanatophoric dwarfism, diaphragmatic hernia, congenital cystic adenomatoid malformation and pleural effusions
- Reduced fetal movements – pulmonary hypoplasia occurs in congenital myotonic dystrophy, spinal muscular atrophy and other congenital myopathies

Outcome with pulmonary hypoplasia depends on the severity and the underlying cause.

### **Congenital diaphragmatic hernia**

- Most common congenital abnormality of the respiratory system – incidence is 1 in 2500–3500 births
- Twice as common in males
- Other congenital malformations are common: 30% have karyotype abnormalities and 17% have other lethal abnormalities; 39% have abnormalities in other systems – malrotation occurs in 20%; those with other congenital abnormalities have double the mortality rate
- 90% are Bochdalek or posterolateral hernias
- 85–90% are left sided
- Bilateral pulmonary hypoplasia occurs – ipsilateral > contralateral
- Usually diagnosed on routine antenatal ultrasound. May present with polyhydramnios. Those who have a normal routine antenatal ultrasound scan are likely to have a better outcome because the hernia usually occurs later, allowing for reasonable lung growth. *In utero* repair and tracheal plugging have been attempted but with variable outcomes
- Respiratory distress (usually severe), heart sounds on the right side of the chest, bowel sounds on the left side, a scaphoid abdomen and vomiting may be found at birth. Less severe cases may not present initially but develop increasing respiratory distress over the first 24 hours as the gut becomes more air filled. Differential diagnosis is congenital cystic adenomatoid malformation (or even pneumothorax)

### **During resuscitation**

- Bag-and-mask positive-pressure ventilation should be avoided
- Wide-bore nasogastric tube should be placed as soon as possible to deflate gut and to confirm diagnosis, and therefore distinguish between differential diagnoses of congenital cystic adenomatoid malformation or pneumothorax on subsequent chest radiograph
- Consider paralysing baby to avoid air swallowing and to reduce the risk of pneumothorax

### **Surgical management**

- There is some evidence to suggest that stabilizing the baby before surgery improves outcome
- Malrotation is corrected if present; the diaphragmatic defect is usually closed with a synthetic patch

### **Postoperative care**

- High-frequency oscillation, nitric oxide or ECMO may be of benefit, but evidence for routine use of these is lacking
- Mortality rate overall is approximately 40%
- Survivors may have problems associated with underlying pulmonary hypoplasia

### **Congenital cystic adenomatoid malformation (CCAM)**

- Rare, abnormal proliferation of bronchial epithelium, containing cystic and adenomatoid portions
- Lower lobes affected more frequently
- May disappear or become smaller spontaneously before or after birth
- Differential diagnosis is congenital diaphragmatic hernia

- Prognosis worse with associated hydrops, preterm birth and with type 3 lesions
- Recurrent infection and malignant change have been described

There are three types.

### *Type 1 CCAM*

- Single or small number of large cysts
- Most common type (50% cases)
- May cause symptoms by compression or may be asymptomatic initially
- Good prognosis after surgery

### *Type 2 CCAM*

- Multiple small cysts
- Usually cause symptoms by compression of surrounding normal lung
- Prognosis variable

### *Type 3 CCAM*

- Airless mass of very small cysts giving the appearance of a solid mass
- Worst prognosis

## **Congenital lobar emphysema**

- Affected lobe is overinflated
- Left upper lobe is most commonly affected (also right middle and upper lobes); rare in lower lobes
- More common in boys
- Associated with congenital heart disease in approximately one in six cases (usually as a result of compression of airways by aberrant vessels)
- Unaffected lobes in affected lung are compressed
- Mediastinal shift and compression of the contralateral lung may also occur
- Presents with signs of respiratory distress, wheezing, chest asymmetry and hyperresonance
- Chest radiograph shows hyperlucent affected lobe  $\pm$  compression of other lobes
- Reduced ventilation and perfusion of the affected lobe is seen on a ventilation–perfusion scan in more severe cases
- Surgical correction of underlying vascular abnormalities or resection of the affected lobe may be required but symptoms and signs may resolve following bronchoscopy

## **Chylothorax**

- Effusion of lymph into the pleural space as a result of either:
  - Underlying congenital abnormality of the pulmonary lymphatics
  - Iatrogenic abnormality after cardiothoracic surgery
- Diagnosis by antenatal ultrasound scan allows antenatal drainage by insertion of intercostal drains, which may reduce the risk of pulmonary hypoplasia and facilitate resuscitation after birth
- Ventilatory support may be required postnatally, along with intermittent intercostal drainage
- Volume of chyle can be reduced by using a medium-chain triglyceride milk formula or avoiding

enteral feeds for up to several weeks as the underlying abnormality resolves with time; protein and lymphocyte depletion may complicate this

- Surgical treatment is needed for the small number of cases that do not resolve spontaneously

### 3.7 Chest wall abnormalities

#### **Asphyxiating thoracic dystrophy**

- Autosomal recessive
- Variable severity
- Short ribs with bell-shaped chest
- May have polydactyly and other skeletal abnormalities also
- Long-term prognosis good in infants who survive >1 year

#### **Ellis–van Creveld syndrome**

- Autosomal recessive
- Short ribs, polydactyly, congenital heart disease, cleft lip and palate
- Pulmonary hypoplasia is usually not severe and symptoms improve later

#### **Short-rib polydactyly syndromes**

- Four variants – all autosomal recessive
- Death from severe respiratory insufficiency occurs in the neonatal period

#### **Thanatophoric dysplasia**

- Usually sporadic
- Very short limbs – femur radiograph described as ‘telephone handle’ shape
- Very small, pear-shaped chest
- Death from lung/chest hypoplasia occurs in the neonatal period

#### **Camptomelic dysplasia**

- Autosomal recessive
- Very bowed, shortened long bones
- Death from respiratory insufficiency usually occurs in childhood

### 3.8 Upper airway obstruction

Neonates are obligate nasal breathers.

## **Choanal atresia**

- Incidence approximately 1:8000
- More common in girls
- Occurs as a result of a failure of breakdown of bucconasal membrane
- May be unilateral or bilateral, bony or membranous
- 60% associated with other congenital abnormalities including the CHARGE association: C = colobomas, H = heart defects, A = atresia of choanae, R = retarded growth and development, G = genital hypoplasia in males, E = ear deformities
- Presents at birth with respiratory distress and difficulty passing a nasal catheter. Oral airway insertion relieves respiratory difficulties. Diagnosis confirmed by contrast study or CT scan
- Surgical correction by perforating or drilling the atresia requires postoperative nasal stents

## **Pierre Robin sequence**

- Consists of protruding tongue, small mouth and jaw, and cleft palate
- Incidence approximately 1:2000
- Problems include obstructive apnoea, difficulty with intubation and aspiration
- To maintain airway patency and prevent obstructive apnoea, prone position should be used initially; if this fails an oral airway should be inserted. Intubation may be needed in severe cases who may eventually require tracheostomy
- Glossopexy and other surgical procedures have been attempted with some degree of success
- Gradual resolution of airway problems occurs as partial mandibular catch-up growth progresses during the first few years of life

## **Laryngomalacia**

- Most common cause of stridor in the first year of life
- Inspiratory stridor increases with supine position, activity, crying and upper respiratory tract infections
- Usually resolves during the second year of life
- Upper airway endoscopy is merited if persistent accessory muscle use occurs, with recurrent apnoea or faltering growth

## **Subglottic stenosis**

- May be congenital but usually acquired

### **Risk factors for acquired subglottic stenosis**

- Prematurity
- Recurrent reintubation
- Prolonged intubation
- Traumatic intubation

- Inappropriately large or small endotracheal tube
- Black babies (keloid scar formation)
- Oral as opposed to nasal intubation (this is a theoretical but unproven factor)
- Gastro-oesophageal reflux
- Infection

Severity is categorized by the Myer–Cotton staging:

- Grade 1 – <50% obstruction
- Grade 2 – 51–70% obstruction
- Grade 3 – 71–99% obstruction
- Grade 4 – total obstruction

Systemic steroids may facilitate extubation in mild to moderately severe subglottic stenosis. Laser or cryotherapy to granulomatous tissue seen on upper airway endoscopy may also be of benefit in these cases. Severely affected babies require surgery – anterior cricoid split (laryngotracheal reconstruction) or tracheostomy.

## Tracheomalacia

- Causes expiratory stridor
- Usually caused by extrinsic compression – most commonly as a result of vascular rings
- Also associated with tracheo-oesophageal fistula
- Surgical treatment of underlying pathology usually leads to resolution, but tracheostomy and positive-pressure ventilation or CPAP (continuous positive airway pressure) may be required

## 3.9 Principles of mechanical ventilation in neonates

- Aims are to:
  - ensure adequate oxygenation
  - adequately remove carbon dioxide to prevent respiratory acidosis
  - minimize the risk of lung injury (VILI or ventilator-induced lung injury)
- Pressure-limited, time-cycled ventilation (PLV) is used most commonly via either an oral or a nasal endotracheal tube. Patient-trigger modes may improve synchronization with the baby's own respiratory efforts, thus improving oxygenation, reducing the risk of air leak and facilitating weaning from the ventilator
- Volume-targeted ventilation (VTV) is now being used more commonly because of advances in ventilator technology, along with recent evidence from RCTs suggesting a reduction in several important clinical outcomes with VTV compared with PLV, including:
  - Combined death or bronchopulmonary dysplasia (BPD)
  - Pneumothorax
  - Hypocapnia
  - Combined periventricular leukomalacia (PVL) or severe intraventricular haemorrhage (IVH)

- Time on ventilator
- High-frequency oscillation may be used initially for any cause of neonatal respiratory failure, but is most often used as ‘rescue’ in severe cases where conventional ventilation has failed
- Nasal CPAP is often used in preterm babies once extubated. This maintains functional residual capacity and reduces the work of breathing

### 3.10 Extracorporeal membrane oxygenation

A membrane ‘lung’ is used to rest the lungs and allow them to recover in severe respiratory failure. Extracorporeal membrane oxygenation (ECMO) may be:

- Venoarterial (VA) – blood removed from right atrium (usually via right internal jugular vein) and returned via a common carotid artery
- Venovenous (VV) – a double-lumen, right atrial cannula is used

ECMO should be considered in severe neonatal respiratory failure if:

- Lung disease is reversible
- Infant is >35 weeks’ gestation
- Weight > 2 kg
- Cranial ultrasound scan shows no intraventricular haemorrhage > grade 1
- No clotting abnormality
- Oxygenation index >40 (see below)

**Oxygenation index (OI)** is used to quantify the degree of respiratory failure. It is measured as:

$$OI = (\text{Mean airway pressure} \times FiO_2 \times 100) \div PO_2$$

where mean airway pressure is in cmH<sub>2</sub>O,  $FiO_2$  (fractional inspired oxygen) is a fraction and  $PO_2$  is in mmHg (note that to convert kPa to mmHg, multiply by 7.6).

- OI >25 indicates severe respiratory failure
- OI >40 indicates very severe respiratory failure with a predicted mortality rate of >80% with conventional treatment – therefore consideration to refer for ECMO is appropriate

Other measures of the degree of respiratory failure that can be used include:

- **Alveolar–arterial oxygen difference (A–aDO<sub>2</sub>)**
  - $A-aDO_2 = (716 \times FiO_2) - PCO_2/0.8 - PO_2$
  - A normal A–aDO<sub>2</sub> is <50 mmHg.
  - If >600 mmHg for successive blood gases over 6 hours, then there is severe respiratory failure with predicted mortality rate >80% with conventional treatment
- **Ventilation index (VI)** =  $PCO_2 \times RR \times PIP/1000$ , where RR is the respiratory rate and PIP is the

peak inspiratory pressure:

- VI > 70 indicates severe respiratory failure
- VI > 90 indicates very severe respiratory failure – suitable for consideration of ECMO

## 4. CARDIOVASCULAR PROBLEMS

### 4.1 Patent ductus arteriosus (PDA)

- Uncommon in term infants after 1–2 days
- Often presents around third day of life in VLBW infants because left-to-right shunt increases as pulmonary vascular resistance falls; approximately 40% of VLBW infants with surfactant deficiency have clinically significant PDA on day 3 of life
- Clinical signs – systolic or continuous murmur, bounding pulses, wide pulse pressure, active precordium, and possibly signs of cardiac failure and reduced lower body perfusion
- A clinically significant PDA in VLBW infants is associated with an increased risk of:
  - Pulmonary haemorrhage
  - Chronic lung disease
  - IVH
  - Necrotizing enterocolitis
  - Mortality
- Early treatment of PDA with indometacin has been shown to reduce NEC and chronic lung disease
- Ibuprofen is likely to be equally effective in closing PDA but has fewer side effects than indometacin (less NEC and transient renal failure)

### 4.2 Hypotension

#### Causes of hypotension in neonates

- Hypovolaemia:
  - Antenatal acute blood loss:
    - Placental abruption
    - Placenta praevia
    - Maternofetal haemorrhage
    - Twin-to-twin transfusion (usually not acute)
    - Vasa praevia
  - Postnatal acute blood loss:
    - Internal
      - Intracranial haemorrhage
      - Intra-abdominal haemorrhage
      - Intrathoracic/pulmonary haemorrhage
      - Severe bruising
    - External:



- Dislodged vascular lines
- Excessive water loss:
  - High urine output
  - High insensible losses – common in extreme prematurity
- Third spacing:
  - Hydrops
  - Pleural effusions
  - Ascites
  - Postoperative
- Vasodilatation:
  - Common in preterm infants
  - Sepsis
  - Drug induced (tolazoline, prostaglandins, prostacyclin)
- Cardiogenic:
  - Myocardial dysfunction:
    - Perinatal asphyxia
    - Metabolic acidosis
  - Congenital heart disease:
    - Hypoplastic left heart
    - Other single-ventricle physiological conditions
  - Arrhythmias:
    - Supraventricular tachycardia
    - Complete heart block
- Reduced venous return:
  - Pulmonary air leak
  - Pericardial effusion/tamponade
  - Lung hyperinflation (more common in high-frequency oscillation or with high positive end-expiratory pressure [PEEP])

## 4.3 Hypertension

### Causes of hypertension in neonates

- Vascular:
  - Renal artery thrombosis (associated with umbilical artery catheterization)
  - Aortic thrombosis (associated with umbilical artery catheterization)
  - Renal vein thrombosis (more common in infants of mothers with diabetes)
  - Coarctation of aorta
  - Middle aortic syndrome
- Renal:
  - Obstructive uropathy
  - Dysplastic kidneys
  - Polycystic kidney disease

- Renal tumours
- Intracranial hypertension
- Endocrine:
  - Congenital adrenal hyperplasia
  - Hyperthyroidism
  - Neuroblastoma
  - Pheochromocytoma
- Drug induced:
  - Systemic steroids
  - Inotropes
  - Maternal cocaine

## 4 Cyanosis in the newborn

### Causes of cyanosis in neonates

- Congenital cyanotic heart disease:
  - Transposition of the great arteries
  - Pulmonary atresia
  - Critical pulmonary stenosis
  - Severe tetralogy of Fallot
  - Tricuspid atresia
  - Ebstein anomaly
  - Truncus arteriosus
  - Total anomalous pulmonary venous drainage
  - Hypoplastic left heart syndrome
- Persistent pulmonary hypertension of the newborn
- Respiratory disease
- Methaemoglobinaemia:
  - Arterial  $PO_2$  is normal
  - Can be congenital:
    - NADH-methaemoglobin reductase deficiency (autosomal recessive)
    - Haemoglobin M (autosomal dominant)
  - Can be iatrogenic:
    - Secondary to nitric oxide therapy
    - Nitrate or nitrite ingestion
  - Treat with intravenous methylene blue
- Acrocyanosis and facial bruising also give the appearance of cyanosis

## 5. GASTROENTEROLOGY AND NUTRITION

### 5.1 Necrotizing enterocolitis

Incidence varies – occurs in about 10% of VLBW infants.

## **Risk factors**

- Prematurity
- Antepartum haemorrhage
- Perinatal asphyxia
- Polycythaemia
- PDA
- PROM

Early enteral feeding has also been suggested because NEC rarely occurs in infants who have not been fed. However, RCTs suggest that early feeding with small amounts of breast milk is beneficial. The incidence of NEC in preterm infants is 6–10 times higher in those fed formula milk compared with those given breast milk. There is some evidence that enteral vancomycin before initiating milk feeds reduces the incidence of NEC.

The severity of NEC can be classified using the Bell staging:

### **Stage 1 – suspected NEC**

- General signs – temperature instability, lethargy, apnoea
- Increased gastric aspirates, vomiting, abdominal distension

### **Stage 2 – confirmed NEC**

- Stage 1 signs, plus
- Upper or lower gastrointestinal bleeding
- Intramural gas (pneumatosis intestinalis) or portal vessel gas on abdominal radiograph

### **Stage 3 – severe NEC**

- Stage 1 and 2 signs, plus
- Signs of shock, severe sepsis and/or severe gastrointestinal haemorrhage
- Bowel perforation

## **Complications**

- Perforation occurs in 20–30% of confirmed NEC cases
- Overwhelming sepsis
- Disseminated intravascular coagulation (DIC)
- Strictures – occur in approximately 20% cases of confirmed NEC
- Recurrent NEC – occurs in <5% cases (consider Hirschsprung disease)

- Short-bowel syndrome after extensive resection
- Lactose intolerance

## Medical management

- Cardiorespiratory support as required
- Stop enteral feeds for 7–14 days (depending on the severity of illness)
- Nasogastric tube on free drainage
- Give intravenous fluids/total parenteral nutrition (TPN)
- Give intravenous antibiotics
- Treatment of thrombocytopenia, anaemia, DIC
- Serial abdominal radiographs (to exclude perforation)

## Surgical management, may include

- Placement of peritoneal drain
- Early laparotomy – with resection of bowel  $\pm$  ileostomy/colostomy; indications for early surgery include perforation or failing medical management
- Late laparotomy  $\pm$  bowel resection; most common indication is stricture formation confirmed with contrast radiographs

## 5.2 Composition of infant milks

	Breast	Term formula	Preterm formula	Cows' milk
Carbohydrate (g/100 ml)	7.4	7.2	8.6	4.6
Protein (g/100 ml)	1.1	1.5	2.0	3.4
Fat (g/100 ml)	4.2	3.6	4.4	3.9
Sodium (mmol/100 ml)	6.4	6.4	14	23
Potassium (mmol/100 ml)	15	14	19	40
Calcium (mmol/100 ml)	8.5	10.8	18	30
Phosphate (mmol/100 ml)	5	10.6	13	32
Calories (per 100 ml)	70	65	80	67

Note that cows' milk has an increased casein:lactalbumin ratio (4:1 compared with 2:3 in breast milk).

## 5.3 Breast-feeding

### Physiology

- A surge in maternal prolactin (from the anterior pituitary) occurs immediately postpartum, which stimulates milk production
- Suckling stimulates prolactin receptors in the breast and oxytocin release (from the posterior pituitary). Oxytocin facilitates the 'let-down' reflex by contraction of breast myoepithelial cells
- Colostrum is produced over the first 2–4 days. Subsequent milk production is controlled mainly by the amount of suckling or expression

# **Benefits of breast-feeding**

See Chapter 10, [Section 2.3](#).

## **Complications**

- Mother – breast engorgement, breast abscess, poor milk production
- Baby – poor weight gain/initial excessive weight loss, breast milk jaundice

## **Drugs contraindicated in breast-feeding mothers**

- Amiodarone
- Antimetabolites (chemotherapy drugs)
- Atropine
- Chloramphenicol
- Dapsone
- Doxepin
- Ergotamine
- Gold
- Indometacin
- Iodides
- Lithium
- Oestrogens (decrease lactation)
- Opiates (high dose should be avoided but weaning to a low dose may facilitate withdrawal in infant)
- Phenindione
- Vitamin D (risk of hypercalcaemia with high dose)

## **Maternal drugs that should be used with caution/monitoring if breast-feeding**

- Some antidepressants
- Some antihistamines
- Carbamazepine
- Carbimazole
- Clonidine
- Co-trimoxazole
- Ethambutol
- Histamine antagonists
- Isoniazid
- Gentamicin
- Metronidazole (makes milk taste bitter)
- Oral contraceptives
- Phenytoin

- Primidone
- Theophylline
- Thiouracil

If in doubt refer to *British National Formulary* or discuss with a pharmacist.

## 5.4 Fluid and nutritional requirements in neonates

Well term babies require little in the way of fluid and calorie intake during the first few days of life. Subsequently, over the next few months of life, there is an average fluid intake of approximately 150 ml/kg per 24 hours but this may vary considerably.

Sick or preterm babies are likely to have reduced but variable fluid requirements, and initial fluid and electrolyte provision should facilitate postnatal weight loss with negative water and sodium balance. Failure to do this is likely to increase the risk of complications such as PDA, pulmonary haemorrhage, NEC and chronic lung disease. Close monitoring of fluid balance and individualized fluid and electrolyte prescription using daily weight, urine output, serum sodium and creatinine are essential, particularly in sick, extremely preterm infants.

Daily nutritional requirements per kilogram for stable, growing, preterm babies are approximately as follows:

- Protein – 3.0–3.8 g
- Energy – 110–120 kcal
- Carbohydrates – 3.8–11.8 g
- Fat – 5–20% of calories
- Sodium – 2–3 mmol
- Potassium – 2–3 mmol
- Calcium – 2–3 mmol
- Phosphate – 1.94–4.52 mmol
- + other minerals (iron, zinc, copper etc.), trace elements (selenium, manganese etc.) and vitamins

## 5.5 Parenteral nutrition

This may be partial, if the baby takes some enteral feeds, or it may be TPN. Indications for TPN include milk intolerance, poor gut motility (common in extreme prematurity), NEC, postoperative (congenital malformations, NEC, etc.).

Parenteral nutrition consists of:

- Protein – up to 3.5 g/kg per day of amino acids (mainly essential amino acids)
- Carbohydrates – up to 18 g/kg per day. Parenteral nutrition should be given via a central venous line if dextrose concentration >12.5%

- Lipids – soya bean oil emulsions (e.g. Intralipid) provide essential fatty acids, a concentrated source of calories and a vehicle for delivering fat-soluble vitamins; 20% Intralipid is tolerated better than 10%. Regular monitoring of plasma lipid levels is recommended. SMOF lipid is a newer preparation which contains soya oil, medium-chain triglycerides, olive oil and fish oils and has been shown to improve liver function compared with a pure soya-bean oil preparation
- Water
- Minerals – sodium, potassium, calcium, phosphate, magnesium
- Trace elements – zinc, copper, manganese, selenium, etc.
- Water-soluble vitamins
- Fat-soluble vitamins

Complications of parenteral nutrition in neonates include:

- Sepsis – mainly intravenous line related (bacterial/fungal)
- Intravenous line extravasation
- Venous thrombosis (line related)
- Fluid/electrolyte imbalance
- Hyperlipidaemia
- Nutritional deficiencies
- Cholestatic jaundice

See also Chapter 10, [Section 3.3](#).

## 5.6 Congenital abnormalities of the gastrointestinal system

### Oesophageal atresia and tracheo-oesophageal fistula

- Occurs as a result of the failure of development of the primitive foregut
- Incidence is approximately 1:3000:
  - 85% – blind proximal oesophageal pouch with a distal oesophageal to tracheal fistula
  - 10% – oesophageal atresia without fistula
  - 5% – proximal ± distal fistula

### Clinical presentation

- Polyhydramnios
- Excessive salivation
- Early respiratory distress
- Abdominal distension
- Vomiting/choking on feeds
- Inability to pass nasogastric tube
- Absence of gas in gut on radiograph if no tracheo-oesophageal fistula
- Other anomalies in 30–50% – VACTERL (vertebral, anal, cardiac, tracheo-oesophageal fistula, ears, renal, limb), rib anomalies, duodenal atresia

- Prematurity common

## Management

- Respiratory support as needed
- Riplogle tube (large-bore, double-lumen suction catheter) on continuous suction is placed in the proximal oesophageal pouch
- Surgical management includes early division of the fistula and early or delayed oesophageal anastomosis. This depends on the distance between the two ends of atretic oesophagus – for wide gaps, delayed anastomosis to allow growth may improve outcome. Cervical oesophagostomy or colonic transposition may also be used in this situation.

**H-type tracheo-oesophageal fistula** (tracheo-oesophageal fistula without oesophageal atresia) is much less common and is usually not associated with preterm birth or other severe anomalies. It may present in the neonatal period or later with respiratory distress associated with feeding, or recurrent lower respiratory infections.

## Duodenal atresia

- Approximately 70% are associated with other congenital anomalies (trisomy 21, congenital heart disease, malrotation, etc.)
- Often diagnosed antenatally with ultrasound ‘double-bubble’ or polyhydramnios
- Usually presents postnatally with bilious vomiting

## Malrotation

- Occurs as a result of incomplete rotation of the midgut in fetal life resulting in intermittent and incomplete duodenal obstruction by Ladd bands
- Associated with diaphragmatic hernia, duodenal and other bowel atresias and situs inversus
- Presents with bilious vomiting and some abdominal distension with sudden deterioration in the event of midgut volvulus
- Upper gastrointestinal contrast studies show the duodenal–jejunal flexure on the right of the abdomen with a high caecum

## Meconium ileus

- Most common presentation of cystic fibrosis in neonates (10–15% cases)
- >90% of babies with meconium ileus have cystic fibrosis, so genetic testing for all common mutations and serum immunoreactive trypsin must be used for confirmation
- May present with antenatal perforation, peritonitis and intra-abdominal calcification or postnatally with intestinal obstruction
- Water-soluble contrast enemas may lead to resolution of meconium ileus
- Important to distinguish between meconium ileus and meconium plug – with meconium plug, symptoms usually resolve after passage of plug and the problem is not associated with cystic



fibrosis

## **Anorectal atresia**

- May have other features of VACTERL association
- May be high or low with the puborectalis sling differentiating – more likely to be a low lesion in girls
- Colostomy is needed for all high atresias
- Renal tract ultrasound scan, micturating cystogram  $\pm$  cystoscopy are needed to exclude rectovaginal, rectourethral or rectovesical fistula or other urinary tract anomaly
- High atresias often have problems with faecal incontinence, whereas those with intermediate/low lesions usually have good outcomes

## **Hirschsprung disease**

- Occurs as a result of an absence of ganglion cells in either a short or long segment of the bowel; the rectum and sigmoid colon are most often affected but cases extending to the upper GI tract have been described
- May present with delayed passage of meconium ( $>24$  hours), bowel obstruction relieved by rectal examination (may be explosive!), enterocolitis or later constipation
- Diagnosis is made by rectal biopsy
- Regular rectal washouts are required before temporary colostomy formation (usually reversed at 6 months)

## **Exomphalos (omphalocele)**

- Results from failure of the gut to return into the abdominal cavity in the first trimester
- The defect is covered by peritoneum which may be ruptured at birth
- Approximately 75% cases have other congenital anomalies – trisomies, congenital heart disease, Beckwith–Wiedemann syndrome
- Primary or staged surgical closure is required
- Topical application of silver sulfadiazine (Flamazine) to promote granulation and epithelialization of the peritoneal covering of the exomphalos before delayed surgical closure has been shown to produce good outcomes

## **Gastroschisis**

- Incidence in the UK is rising (approximately 1 in 2000 live births) and is now nearly five times as common as exomphalos
- Aetiology unknown but strong association with teenage pregnancy and possibly smoking and recreational drugs
- Much less likely to be associated with other congenital anomalies
- Bowel is not covered by peritoneum and therefore becomes stuck together with adhesions; this leads to functional atresias and severe intestinal motility problems after surgical repair of the

abdominal wall defect

- Prognosis is mostly good

## 6. NEUROLOGICAL PROBLEMS

### 6.1 Peri-intraventricular haemorrhage

The germinal matrix or layer occurs in the caudothalamic notch of the floor of the lateral ventricles. It is the site of origin of migrating neuroblasts from the end of the first trimester onwards. By 24–26 weeks' gestation this area has become highly cellular and richly vascularized. This remains so until approximately 34 weeks' gestation, by which time it has rapidly involuted. The delicate network of capillaries in the germinal matrix is susceptible to haemorrhage, which is likely to occur with changes in cerebral blood flow. Preterm infants have decreased autoregulation of the cerebral blood flow, which contributes to the pathogenesis. In term infants peri-IVH (PIVH) may originate from the choroid plexus.

#### Risk factors for PIVH

- Prematurity (28% at 25 weeks; <5% after 30 weeks)
- Lack of antenatal maternal steroids
- Sick and needing artificial ventilation
- Hypercapnia
- Metabolic acidosis
- Pneumothoraces (as a result of increased venous pressure or possibly related to surge in blood pressure when drained)
- Abnormal clotting
- Rapid volume infusions (particularly with hypertonic solutions) or increases in blood pressure with inotropes
- Perinatal asphyxia
- Hypotension
- PDA

#### Timing of PIVH

- $\geq 50\%$  in first 24 hours
- Approximately 10–20% days 2–3
- Approximately 20–30% days 4–7
- Approximately 10% after the first week

#### Classification of PIVH

- Grade 1 – germinal matrix haemorrhage
- Grade 2 – IVH without ventricular dilatation

- Grade 3 – IVH with blood distending the lateral ventricle
- Grade 4 – echogenic intraparenchymal lesion associated with PIVH; previously this was thought to be an extension of bleeding from the lateral ventricles into the surrounding periventricular white matter but it is likely to be venous infarction

Several classification systems have been described. The most widely accepted is that of Papile (above). It may, however, be better to use a more descriptive classification.

## Prevention of PIVH

The following have been shown to reduce the incidence of PIVH:

- Antenatal steroids
- Maternal vitamin K
- Indomethacin (but long-term neurodisability is not reduced)

The following have been evaluated but have no proven benefit:

- Vitamin E
- Ethamsylate
- Phenobarbital
- Fresh frozen plasma (FFP)
- Nimodipine

## Clinical presentation of PIVH

- Grades 1 and 2 PIVH present silently and are detected by routine ultrasonography
- Grade 3 PIVH occasionally presents with shock from blood volume depletion
- Grade 4 PIVH may present similarly and occasionally with neurological signs (seizures, hypotonia, bulging fontanelle)

## Sequelae of PIVH

### Death

- Mortality rate was 59% in one series of large grade 4 PIVH

### Post-haemorrhagic ventricular dilatation (PHVD)

- Defined as lateral ventricle measurement >4 mm above 97th centile following PIVH
- A minority of PIVH cases develop PHVD – risk is higher with more severe lesions
- Spontaneous resolution occurs in approximately 50% of cases of PHVD; the rest develop hydrocephalus (i.e. PHVD that requires drainage)
- As a sequel to PIVH, **communicating hydrocephalus** (as a result of malfunction of the arachnoid

villi) is more common than **non-communicating hydrocephalus** (as a result of blockage of the cerebral aqueduct)

- Early, aggressive intervention with repeated lumbar puncture and/or ventricular taps has not been shown to be of benefit; drainage should probably be considered if the baby is symptomatic, cerebrospinal fluid (CSF) pressure is very high ( $>12$  mmHg or 15.6 cmCSF; normal CSF pressure is 5.25 mmHg or 6.8 cmCSF) or head circumference and/or ventricular measurement on ultrasound scan is increasing rapidly
- Timing of surgical intervention with CSF reservoir or ventriculoperitoneal shunt insertion is controversial
- Drug treatment with acetazolamide with or without diuretics has been shown to be ineffective
- Intraventricular fibrinolytic administration is experimental

## **Adverse neurodevelopment**

- Cerebral palsy is the most common adverse neurodevelopmental sequel but other and global problems may also arise
- Approximate risk of adverse outcome is as follows:
  - 4% in grades 1 and 2 PIVH if ventricles remain normal size
  - 50% in grade 2 with PHVD or grade 3 PIVH
  - 75% in PIVH requiring shunt
  - 89% with large, grade 4 lesions (difficult to quantify because pathology is varied)

## **6.2 Periventricular leukomalacia**

- PVL is haemorrhagic necrosis in the periventricular white matter that progresses to cystic degeneration and subsequent cerebral atrophy. It is often associated with infection (chorioamnionitis) and may be cytokine mediated. Hypoxia and ischaemia may also play a role. On ultrasound scan, the initial necrosis appears as echogenicity (often described as ‘flare’) within a few days of the causative insult. This sometimes resolves but it may become a multicystic area after 1–4 weeks. The long-term neurological effects are usually bilateral, although initial ultrasound appearances are sometimes unilateral
- Long-term neurodevelopmental effects of cystic PVL are:
  - Spastic diplegia or tetraplegia ( $>90\%$ )
  - Learning difficulties
  - Seizures (including infantile spasms)
  - Blindness
- Worse outcomes are associated with subcortical PVL. Transient periventricular echodensities are associated with a risk of spastic diplegia of approximately 5–10% if they persist for more than 7–14 days

## **6.3 Neonatal encephalopathy**

Neonatal encephalopathy is also known as hypoxic–ischaemic encephalopathy. The underlying cause is often unclear but it may originate antenatally, peripartum or postnatally, hence the term ‘perinatal asphyxia’. Other evidence of organ dysfunction often occurs concurrently, especially if the insult occurs close to the time of birth. Placental insufficiency is a factor in the vast majority of cases.

## Pathophysiology of neonatal encephalopathy

Primary and secondary neuronal injuries have been described:

- **Primary neuronal injury** results from energy failure because of the inefficiency of anaerobic respiration to produce high-energy phosphocreatine and ATP. Glucose utilization increases and lactic acid accumulates. Energy failure and myocardial dysfunction further exacerbate this, leading to ion pump failure ( $\text{Na}^+/\text{K}^+$ -ATPase) and neuronal death as a result of cerebral oedema
- **Secondary or delayed neuronal injury** occurs because there are marked changes in cerebral blood flow with initial hypoperfusion and then reperfusion after resuscitation. This is associated with neutrophil activation and is exacerbated by prostaglandins, free radicals and other vasoactive substances. Excitatory amino acid neurotransmitters such as glutamate and *N*-methyl D-aspartate (NMDA) lead to excessive calcium influx and delayed neuronal death. The cellular mechanism for this may be necrosis or apoptosis (programmed cell death)

## Clinical presentation

This can be staged according to the scheme suggested by Sarnat and Sarnat:

- Stage 1 – hyperalert, irritable; normal tone and reflexes; signs of sympathetic overactivity; poor suck; no seizures; symptoms usually resolve <24 hours; good outcome in approximately 99%
- Stage 2 – lethargic, obtunded, decreased tone and weak suck and Moro reflexes; seizures are common; approximately 75–80% have good outcomes; this is less likely if symptoms persist for >5 days
- Stage 3 – comatose with respiratory failure; severe hypotonia and absent suck and Moro reflexes; seizures less common but EEG abnormalities common – flat background or burst suppression; over 50% die and majority of survivors have major handicap

## Management

Management is largely supportive but recent evidence supports the use of therapeutic hypothermia in babies >35 weeks’ gestation.

Therapeutic hypothermia:

- Baby cooled to between 33°C and 35°C by either total body or head-only cooling device
- Maximum benefit likely if cooling starts within 6 hours of birth and is continued for 72 hours, followed by slow warming to normal temperature
- RCTs show that the risk of death or severe neurological problems is significantly reduced

## 6.4 Neonatal seizures

### Causes of seizures in the newborn

- Neonatal encephalopathy
- Cerebral infarction:
  - Usually presents on day 1 or 2
  - Often presents with focal seizures
  - Aetiology uncertain but thrombosis secondary to hypercoagulation tendency is a possibility
  - Outcome good in approximately 50%; the other 50% may develop mono- or hemiplegia or long-term seizure disorder
- Intracranial haemorrhage (massive PIVH, subarachnoid or subdural haemorrhage)
- Birth trauma (head injury equivalent)
- Meningitis
- Other sepsis
- Congenital infection
- Neonatal drug withdrawal
- Fifth-day fits (onset day 3–5, unknown cause, resolve spontaneously)
- Hypoglycaemia
- Hypocalcaemia
- Hypo- or hypermagnesaemia
- Inborn errors of metabolism:
  - Non-ketotic hyperglycinaemia
  - Sulphite oxidase deficiency
  - Biotinidase deficiency
  - Maple-syrup urine disease
  - Pyridoxine dependence
  - Urea cycle defect
  - Organic acidaemias (e.g. methylmalonic acidaemia)
- Structural brain abnormalities (migration disorders, etc.)
- Hydrocephalus
- Polycythaemia
- Neonatal myoclonus – not a true seizure, benign and common in preterm infants

### Management of neonatal seizures

- Investigate for, and treat, underlying condition
- Initial treatment with phenobarbital, followed by midazolam, other benzodiazepines and paraldehyde
- Currently no evidence that suppression of clinical or electrographic seizures improves outcome

## 6.5 Causes of hypotonia in the newborn

### Central causes

- Neonatal encephalopathy
- Intracranial haemorrhage
- Infection – generalized sepsis, meningitis, encephalitis
- Chromosomal abnormalities – trisomy 21, 18 or 13
- Structural brain abnormalities – neuronal migration disorders, etc.
- Metabolic disease – amino and organic acidaemias, urea cycle defects, galactosaemia, non-ketotic hyperglycinaemia, peroxisomal disorders, mitochondrial disorders, congenital disorders of glycosylation, Menkes syndrome
- Drugs – opiates, barbiturates, benzodiazepines, etc.
- Prader–Willi syndrome
- Hypothyroidism
- Early kernicterus

### Spinal cord lesions

- Trauma to the cervical spinal cord during delivery – usually involves traction and rotation with forceps
- Tumours, cysts and vascular malformations of spinal cord

### Neuromuscular disease

- Spinal muscular atrophy
- Congenital myotonic dystrophy
- Congenital myopathies
- Myasthenia gravis

## 6.6 Retinopathy of prematurity

- Retinopathy of prematurity (ROP) consists of vascular proliferation secondary to retinal vasoconstriction. This may progress and lead to fibrosis and scarring
- Prematurity and hyperoxia are known associations, but other factors, including hypoxia, are also implicated
- Babies <32 weeks' gestation at birth and <1500 g birthweight should be screened by ophthalmological examination from 30 weeks' corrected gestational age
- ROP should be described by stage, location, extent and presence of additional disease

### ROP stages

- Stage 1 – demarcation line

- Stage 2 – ridge
- Stage 3 – ridge with extraretinal fibrovascular proliferation
- Stage 4 – subtotal retinal detachment
- Stage 5 – total retinal detachment
- Stages 1 and 2 disease resolves without risk of visual impairment if there is no progression
- Stage 3 disease increases the risk of visual impairment
- Stages 4 and 5 always lead to visual impairment

## **ROP location**

- Zone 1, 2 or 3 (where zone 1 is the most central [i.e. posterior] around the optic disc)
- The risk is greatest if zone 1 is affected

ROP extent is described in terms of the number of clock hours.

Plus disease includes tortuosity of the retinal vessels, pupil rigidity and vitreous haze.

Usually stage 3 plus disease should be treated with either cryotherapy or laser therapy, but location and extent of ROP also determine the need for treatment.

See also [Chapter 20](#).

## **7. GENITOURINARY PROBLEMS**

### **7.1 Congenital abnormalities of the kidneys and urinary tract**

Nephrogenesis (branching and new nephron induction) continues up to 36 weeks' gestation, but glomerular filtration rate is still <5% of adult values at this stage. This increases rapidly in the first week and then more gradually over the next 2 years to adult values.

The renal function of a neonate is limited by:

- Renal blood flow
- Glomerular filtration rate
- Tubular concentrating and diluting ability
- Tubular excretion
- Urine output

More than 90% of neonates pass urine within 24 hours of birth. The collecting ducts have increased sensitivity to antidiuretic hormone (ADH) after birth and urine-concentrating ability increases rapidly.

Preterm infants have immature tubular function, leading to a high fractional excretion of sodium and high sodium intake requirements.



Antenatally, congenital renal abnormalities may present with:

- Oligohydramnios (Potter syndrome if severe)
- Urinary ascites – as a result of obstructive uropathy
- Other abnormalities seen on antenatal ultrasound scan include:
  - Obstructive uropathy – dilated renal tracts
  - Cystic dysplasia/polycystic disease

## **Obstructive uropathy**

### **Posterior urethral valves**

- Mucosal folds in posterior urethra of male infants leading to dilatation of renal tract proximal to obstruction
- Bladder is often hypertrophied
- Diagnosed by micturating cystourogram
- Suprapubic catheter is inserted initially, followed by surgical resection by cystoscopy or vesicostomy, followed by later resection

### **Pelviureteric junction (PUJ) obstruction**

- Usually unilateral
- Diagnosed on antenatal ultrasound scan or presents with abdominal mass
- Gross hydronephrosis is associated with decreased renal function (confirmed with  $^{99m}\text{Tc}$ -labelled MAG-3 (mertiatide) renogram); nephrectomy is usually required. Ureteroplasty is carried out for milder cases

## **Mild renal pelvis dilatation**

- Should be confirmed on postnatal ultrasound scan and investigated with a micturating cystourogram to exclude reflux nephropathy, which is a risk for recurrent urinary tract infection and subsequent scarring

## **Prune-belly syndrome (megacystis–megaureter)**

- Lax abdominal musculature, dilated bladder and ureters, and undescended testes
- Neurogenic bladder
- Usually as a result of abnormalities of lumbosacral spine

## **Ureterocele**

- Dilatation of distal ureter leading to obstruction

## **Urethral stricture**

## **Tumours (neuroblastoma, Wilms tumour)**

See [Chapter 12](#), Sections 11.6 and 11.7.

## **7.2 Haematuria in the newborn**

### **Causes of haematuria in the newborn**

- Urinary tract infection
- Obstructive uropathy
- Acute tubular necrosis
- Renal artery or vein thrombosis
- Renal stones
- Trauma
- Tumours
- Cystic dysplasia and other malformations
- Abnormal clotting

## **7.3 Causes of acute renal failure in neonates**

### **Prerenal**

- Hypotension
- Dehydration
- Indomethacin

### **Renal**

- Cystic dysplasia and infant polycystic kidney disease
- Renal artery/vein thrombosis
- Congenital nephrotic syndrome
- DIC
- Nephrotoxins, e.g. gentamicin

### **Postrenal**

- Obstructive nephropathy

## **7.4 Ambiguous genitalia**

See Section 1.5 for embryology of sexual differentiation.

On examination, note the following:

- If gonads are palpable they are nearly always testes
- Length of phallus – if <2.5 cm stretched length in a term baby it is unlikely that the baby can function as a male
- Severity of hypospadias and fusion of labia
- Other dysmorphic features/congenital abnormalities

The parents should be told that the child's sex is uncertain at this stage and that the genitalia are not normally/completely formed. Prompt diagnosis and appropriate management are essential to resolve this and to exclude or treat congenital adrenal hyperplasia before electrolyte imbalances occur. Also gonadal tumours may be a risk.

## Differential diagnosis

- True hermaphroditism:
  - Testes and ovaries both present (rare)
- Male pseudohermaphroditism – underdevelopment ( $\downarrow$  virilization) of male features:
  - Androgen insensitivity (= testicular feminization) – most common
  - Defects in testosterone synthesis
  - Some forms of congenital adrenal hyperplasia
  - Panhypopituitarism (should be suspected if hypoglycaemia is also present)
  - Defects in testosterone metabolism ( $5\alpha$ -reductase most common)
  - Defects in testicular differentiation (rare)
- Female pseudohermaphroditism – virilization of female:
  - Congenital adrenal hyperplasia – most common enzyme deficiency is 21-hydroxylase deficiency ( $\uparrow$   $17\alpha$ -hydroxyprogesterone)
- Chromosomal abnormalities:
  - 45X/46XY mosaicism (rare)

## Investigations

- Karyotype
- Daily electrolytes until diagnosis is established
- Blood pressure monitoring
- Blood sugar monitoring
- Abdominal ultrasound scan
- Serum hormone assay –  $17\alpha$ -hydroxyprogesterone, 11-deoxycortisol, testosterone, estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone
- Urine steroid profile
- Genitogram/micturating cystourogram

## 8. INFECTION

### 8.1 Bacterial infection

#### **Group B streptococcus (GBS)**

- Up to 20% of pregnant women have genital tract colonization with GBS
- Three serotypes have been identified
- Neonatal GBS infection may be early (within first few days, usually presenting by 24 hours) or late (after first week, usually at 3–4 weeks)
- Early disease often presents with septicaemia and respiratory distress (pneumonia or persistent pulmonary hypertension of the newborn)
- Late disease is usually septicaemia or meningitis – may be vertical or nosocomial transmission; antibiotics given intrapartum or in first few days do not always prevent late GBS disease
- Serotype 3 is more common in late-onset GBS disease or meningitis if this is part of early onset disease

#### ***Escherichia coli***

- Usually causes vertical infections in neonates and is often associated with preterm birth; can also cause nosocomial infection
- K1 capsular antigen is the most common serotype
- Septicaemia and meningitis are the most common presentations if vertically transmitted; urinary tract infections and NEC have been noted in nosocomial *E. coli* sepsis in neonates

#### **Coagulase-negative staphylococci**

- Most common nosocomial pathogen in neonatal intensive care units
- VLBW infants with indwelling catheters are most at risk
- Often resistant to flucloxacillin

#### ***Listeria monocytogenes***

- Gram-positive rod
- Outbreaks have been caused by dairy products, coleslaw, pâté and undercooked meat
- May present with a flu-like illness in pregnant women and then lead to stillbirth or severe neonatal septicaemia and meningitis
- Early and late-onset disease have been noted, similar to GBS
- Early onset disease is associated with preterm birth and ‘meconium’-stained amniotic fluid (which is in fact often pus rather than meconium)
- A maculopapular or pustular rash is typical
- Amoxicillin and gentamicin are the antibiotic combination of choice

#### **Other bacterial pathogens in neonates include**

- *Haemophilus influenzae*
- *Klebsiella* spp.
- *Pseudomonas* spp.
- Pneumococci

## **Risk factors for vertically acquired bacterial sepsis**

- Preterm rupture of membranes
- Prolonged rupture of membranes (>12–24 h)
- Maternal fever (>38°C or other signs of chorioamnionitis, e.g. white cell count >  $15 \times 10^9/l$ )
- Maternal colonization with GBS
- Fetal tachycardia
- Lack of intrapartum antibiotics in the presence of above risk factors
- Foul-smelling amniotic fluid
- Preterm birth/low birthweight
- Twin pregnancy
- Low Apgar scores

## **Risk factors for nosocomial sepsis**

- Prematurity/low birthweight
- SGA infants
- Neutropenia
- Indwelling catheters
- TPN
- Surgery

## **8.2 Congenital viral infection**

### **Cytomegalovirus**

- Member of the Herpesviridae family (DNA virus)
- Transmitted by close personal contact, blood products or breast-feeding. May also be sexually transmitted
- Causes mild symptoms in healthy adults or children
- Up to 1% of pregnancies are affected but symptoms occur in less than 10% of those infected
- Primary infection or reactivation may occur in affected pregnancies
- Symptoms in affected neonates include:
  - IUGR
  - Prematurity
  - Hepatosplenomegaly
  - Thrombocytopenia

- Anaemia
- Jaundice (raised conjugated and unconjugated bilirubin – often prolonged)
- Pneumonitis
- Microcephaly
- Intracranial calcification
- Choroidoretinitis
- Osteitis
- Long-term neurodevelopmental sequelae are common and include cerebral palsy, learning disability, epilepsy, blindness and deafness

## **Diagnosis**

- Rising specific IgG antibodies in mother or baby
- Specific IgM may be raised for up to 16 weeks after primary infection
- Virus can be isolated from urine or throat swab
- Detection of early antigen fluorescent foci (DEAFF) is a newer technique used to detect viral antigen from urine and other body fluids
- Aciclovir has been used with some success in immunosuppressed adults but may be toxic in neonates and is not of proven efficacy

## **Rubella**

First-trimester infection of the fetus results in congenital rubella syndrome. The most common features of this are:

- Congenital heart disease
- Cataracts
- Deafness

IUGR, microcephaly, hepatosplenomegaly, thrombocytopenia, choroidoretinitis and osteitis may also occur similar to congenital CMV infection. Immunization of children has virtually eradicated congenital rubella in the UK.

## **Parvovirus**

Parvovirus is a DNA virus. Serotype B19 causes epidemics of erythema infectiosum (‘slapped cheeks’ syndrome or fifth disease) in the winter months. Fetal infection, particularly in the first trimester, leads to severely decreased red cell production and subsequent severe fetal anaemia, resulting in heart failure and non-immune hydrops. Fetal blood can be used to confirm the diagnosis by viral antigen detection with polymerase chain reactions. Fetal blood transfusions may reverse hydrops and improve outcome.

## **Neonatal human immunodeficiency virus**

Vertically transmitted HIV is the most common cause of childhood AIDS. Approximately a third of infections are transmitted across the placenta and two-thirds during birth. Babies of all HIV-positive mothers are also seropositive initially because IgG crosses the placenta. Non-infected infants become negative by 9 months. There is no evidence of HIV causing an embryopathy. Babies are usually initially asymptomatic but may present with hepatosplenomegaly and thrombocytopenia in the neonatal period. The following increase the risk of vertical transmission:

- Low maternal CD4 count
- High maternal viral load
- Presence of p24 antigen in the mother
- Preterm birth
- Rupture of membranes >4 hours
- Vaginal birth
- No maternal antiretroviral treatment/poor compliance

Maternal zidovudine (AZT) during the third trimester and labour and given to the infant for 6 weeks postnatally reduces transmission rate from 25.5% to 8.3%. Other measures leading to avoidance of above risk factors have been shown to reduce risk further to well under 5%.

Immunizations should be given routinely to infants of HIV-positive mothers with the following cautions:

- Give killed (Salk) rather than live (Sabin) polio vaccine
- Give BCG early

## **Hepatitis B virus**

- Babies of women who are hepatitis B surface antigen (HbsAg) positive or who have active hepatitis B during pregnancy should all receive hepatitis B vaccine in the neonatal period, and at 1 and 6 months
- Hepatitis B immunoglobulin should be given within 48 hours of birth to all babies of mothers who are HbsAg positive apart from those with the hepatitis B e antibody
- Breast-feeding is not contraindicated

## **8.3 Fungal and protozoal infections**

### ***Candida albicans***

*Candida* sp. may cause superficial mucocutaneous infection or severe systemic sepsis, particularly in extremely preterm infants. Amphotericin, flucytosine and fluconazole may be used to treat severe fungal infections.

### **Toxoplasmosis**

- *Toxoplasma gondii* is a unicellular, protozoan parasite
- Cats are the definitive hosts. Infection of humans occurs following ingestion of sporocysts after handling cat faeces, contaminated vegetables or undercooked meat
- Toxoplasmosis is a mild illness in healthy adults
- Congenital infection is more likely with increasing gestation as the placenta provides less of a barrier with age. However, severe infection becomes less likely, falling from 75% in the first trimester to <5% in the third

Severe congenital toxoplasmosis causes:

- IUGR
- Preterm birth
- Hydrocephalus and sequelae
- Choroidoretinitis
- Intracranial calcification
- Hepatitis
- Pneumonia
- Myocarditis

Babies born with no symptoms may go on to develop choroidoretinitis after months or even years. Serological diagnosis is made by specific IgG and IgM titres. Treatment of affected pregnant women with spiramycin reduces the rate of transmission to the fetus but does not reduce the severity of disease. Affected infants are treated with pyrimethamine and sulfadiazine for up to 1 year.

## 9. NEONATAL ENDOCRINE PROBLEMS

### 9.1 Neonatal hypoglycaemia

Definition – blood glucose  $\leq 2.6$  mmol/l.

Normal term babies commonly have blood sugars <2.6 mmol/l, particularly in the first 24 hours (especially if the baby is breast-fed), but are not at risk of any long-term sequelae because they can utilize alternative fuels (e.g. ketones, lactate). It is therefore unnecessary to perform blood glucose analysis on healthy term babies.

Infants at risk of clinically relevant hypoglycaemia include:

- Those with increased demand/decreased supply, i.e.
  - Preterm
  - IUGR
  - Hypothermia
  - Infection
  - Asphyxia



- Polycythaemia
- Hyperinsulinism:
  - Infant of a mother with diabetes
  - Haemolytic disease of the newborn
  - Transient neonatal hyperinsulinism
  - Beckwith–Wiedemann syndrome
  - Persistent hyperinsulinaemic hypoglycaemia of infancy (previously called nesidioblastosis)
  - Islet cell adenoma
- Endocrinopathies:
  - Pituitary (e.g. growth hormone deficiency, septo-optic dysplasia)
  - Adrenal (e.g. congenital adrenal hyperplasia)
- Carbohydrate metabolism disorders:
  - Glycogen storage disease
  - Galactosaemia
- Amino acidopathies
- Organic acidaemias
- Fat oxidation defects:
  - Deficiencies of medium-chain and very-long-chain acyl-coenzyme A dehydrogenases (MCADD and VLCAD), long-chain hydroxyacyl-coenzyme A dehydrogenase (LCHAD)

Babies at risk of clinically significant hypoglycaemia should be treated immediately with intravenous dextrose (2 ml/kg 10% dextrose followed by intravenous infusion) if blood glucose is  $<1.5$  mmol/l.

## 9.2 Panhypopituitarism

Presents with:

- Persistent hypoglycaemia
- Poor feeding
- Micropenis
- Hyperbilirubinaemia (conjugated)
- Midline facial defects (cleft palate etc.)
- Optic atrophy
- Low growth hormone, cortisol (may cause hyponatraemia) and thyroid-stimulating hormone

## 9.3 Adrenal insufficiency

Causes include:

- Congenital adrenal hyperplasia:
  - Most common cause is 21  $\alpha$ -hydroxylase deficiency (may or may not involve salt loss)
  - May be X-linked or autosomal recessive inheritance
- Smith–Lemli–Opitz syndrome

- Wolman syndrome (liposomal acid lipase deficiency)
- Adrenal haemorrhage
- Secondary causes:
  - Panhypopituitarism
  - Withdrawal from steroid treatment

Management of salt loss is an initial priority, followed by glucocorticoid (hydrocortisone) and mineralocorticoid (fludrocortisone) replacement.

## 10. NEONATAL JAUNDICE

### 10.1 Physiological jaundice

Jaundice becomes visible when serum bilirubin is  $>80\text{--}100\ \mu\text{mol/l}$  and up to 65% term infants become clinically jaundiced. However, only 1.2% become sufficiently jaundiced to require treatment (i.e.  $>340\ \mu\text{mol/l}$ ). Physiological jaundice occurs as a result of:

- Increased haemolysis:
  - Bruising
  - Antibody induced
  - Relative polycythaemia
  - Lifespan of red blood cells (in term infants – 70 days, in preterm infants – 40 days)
- Immature hepatic enzyme systems
- ‘Shunt’ bilirubin from breakdown of non-red blood cell haem pigments
- Enterohepatic circulation

Breast-fed babies have higher maximum serum bilirubin levels and remain jaundiced for longer.

### 10.2 Causes of non-physiological jaundice

Jaundice is considered non-physiological if any of the following are present:

- Onset before 24 hours of age
- Serum bilirubin  $>270\ \mu\text{mol/l}$
- Lasting  $>14$  days ( $>21$  days in preterm infants)
- Associated pathological conditions that are known to cause jaundice

Causes of non-physiological jaundice (unconjugated hyperbilirubinaemia):

- Haemolysis:
  - Isoimmunization (Rh, ABO, other)
  - Spherocytosis, etc.

- Glucose-6-phosphate dehydrogenase or pyruvate kinase deficiency
- Sepsis
- $\alpha$ -Thalassaemia
- Polycythaemia
- Extravasated blood
- Increased enterohepatic circulation
- Endocrine/metabolic
- Rare liver enzyme deficiencies (Crigler–Najjar syndrome, etc.)

## Haemolytic disease of the newborn

May be caused by rhesus D (Rh) incompatibility (mother RhD negative, baby RhD positive) or by other antibodies (c, E, Kell, Duffy, etc.). Approximately 15% of the UK population are RhD negative. Sensitization occurs from previous pregnancy, antepartum haemorrhage, trauma or antenatal procedure.

Prevention of haemolytic disease is by the following:

- Intramuscular anti-D is given after any possible event leading to sensitization in RhD-negative women
- Maternal serum screening for antibodies at booking with re-testing between 28 and 36 weeks for RhD-negative women with no antibodies
- Referral to a specialist fetal medicine centre for all those with significant levels of antibodies; initially antibody levels are measured but correlate poorly with the degree of fetal anaemia above a certain threshold; once this is reached, further monitoring is by ultrasound scanning to detect signs of hydrops, amniocentesis and spectrophotometric estimation of bilirubin in the amniotic fluid or fetal blood sampling to detect anaemia
- Serial fetal blood transfusions in severe cases
- Preterm delivery

## Conjugated hyperbilirubinaemia

Causes of conjugated hyperbilirubinaemia:

- TPN cholestasis
- Viral hepatitis (hepatitis B virus, CMV, herpesvirus, rubella, HIV, Cocksackievirus, adenovirus)
- Other infection (toxoplasmosis, syphilis, bacterial)
- Haemolytic disease (due to excessive bilirubin)
- Metabolic ( $\alpha_1$ -antitrypsin deficiency, cystic fibrosis, galactosaemia, tyrosinaemia, Gaucher disease and other storage diseases, rotor syndrome, Dubin–Johnson syndrome)
- Biliary atresia
- Choledochal cyst
- Bile duct obstruction from tumours, haemangiomas, etc.

Note that levels of conjugated bilirubin  $>25 \mu\text{mol/l}$  should be investigated.

## 10.3 Management of non-physiological unconjugated hyperbilirubinaemia

The aim of management is to reduce the risk of kernicterus and NICE guidelines have been developed recently for this purpose, with treatment thresholds that vary according to clinical risks present.

### Measurement of bilirubin

- Visual inspection alone is not sufficient to estimate the level of bilirubin in a jaundiced baby
- Use of a transcutaneous bilirubinometer is recommended in babies >35 weeks' gestation and >24 hours' old
- Serum bilirubin should be measured if <35 weeks' gestation, <24 hours' old or if transcutaneous level >250  $\mu\text{mol/l}$

Treatment thresholds are lower for babies who are sick, preterm, have evidence of haemolysis or rapidly rising serum bilirubin (>200  $\mu\text{mol/l}$  per 24 h).

### Phototherapy

This is used to treat moderately severe unconjugated hyperbilirubinaemia. Phototherapy photo-oxidizes and isomerizes bilirubin, facilitating increased excretion via urine and bile.

Intensive phototherapy (i.e. concurrent use of more than one phototherapy device) is used for high levels of bilirubin pending exchange transfusion or to avoid the need for exchange transfusion as levels become too close to the threshold for this.

Complications of phototherapy are mainly minor and include:

- Diarrhoea
- Transcutaneous fluid loss
- Rashes

### Exchange transfusion

This is used to treat severe unconjugated hyperbilirubinaemia, often with concomitant anaemia, most commonly as a result of haemolysis. The procedure dilutes bilirubin, removes sensitized red blood cells and corrects anaemia.

Usually a double-volume exchange transfusion is performed via arterial and central venous lines over 1–2 hours, replacing the baby's blood volume twice with donor blood.

Complications of exchange transfusion include:

- Infection and other line-related complications

- Fluid and electrolyte disturbance
- Thrombocytopenia and coagulopathy
- Transfusion reaction

### **Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) (500 mg/kg over 4 h) is recommended as an adjunct to intensive phototherapy and exchange transfusion in haemolytic disease or ABO incompatibility if the serum bilirubin continues to rise rapidly (i.e.  $>200\text{ }\mu\text{mol}$  per 24 h).

## **10.4 Prolonged jaundice**

This is defined as jaundice lasting more than 14 days in term babies and more than 21 days in preterm babies. NICE guidelines recommend that in preterm and term babies with prolonged jaundice:

- Look for pale, chalky stools and/or dark urine that stains the nappy
- Measure the conjugated bilirubin
- Carry out a full blood count, blood group determination, DAT and urine culture
- Ensure that routine metabolic screening has been performed
- Follow expert advice about care for babies with a conjugated bilirubin level  $>25\text{ }\mu\text{mol}$  (see Chapter 12)

## **11. NEONATAL HAEMATOLOGY/COAGULATION PROBLEMS**

### **11.1 Polycythaemia**

See also Chapter 12, Section 10.2.

Definition – haematocrit  $>65\%$ .

### **Causes**

- IUGR
- Maternal diabetes
- Delayed cord clamping
- Twin-to-twin transfusion
- Maternofetal transfusion
- Trisomies (13, 18, 21)
- Endocrine disorders (congenital adrenal hyperplasia, thyrotoxicosis, Beckwith syndrome)

### **Complications**

- Hypoglycaemia

- Jaundice
- NEC
- Persistent pulmonary hypertension of the newborn
- Venous thromboses
- Stroke

## Treatment

Treatment is recommended if the haematocrit is  $>65\%$  and the patient is symptomatic. A partial dilutional exchange transfusion should be carried out using physiological (0.9%) saline.

## 11.2 Haemorrhagic disease of the newborn and vitamin K

- Results from relative deficiency of factors II, VII, IX and X and is prevented by vitamin K
- Breast milk contains inadequate amounts of vitamin K, so the recommendation in the UK is to give all babies either a single intramuscular injection of vitamin K at birth or an oral dose at birth followed by two further oral doses at 1–2 weeks and 6 weeks in those who are predominantly breast-fed
- May be exacerbated by perinatal asphyxia, liver dysfunction and maternal phenytoin or phenobarbital
- Usually presents between days 2 and 6 with gastrointestinal haemorrhage, umbilical stump bleeding, nose bleeds or intracranial haemorrhage
- Prothrombin time and activated partial thromboplastin are prolonged with normal thrombin time and fibrinogen
- Treat with fresh frozen plasma and intravenous vitamin K  $\pm$  blood transfusion
- Late haemorrhagic disease may occur between 8 days and 6 months; intracranial haemorrhage is more common in these cases

## 11.3 Disseminated intravascular coagulation

This may occur in any sick neonate, e.g. those with:

- Sepsis
- Placental abruption or other perinatal events
- NEC
- Meconium aspiration syndrome

Intravascular coagulation leads to thrombocytopenia and coagulopathy as a result of consumption of platelets, clotting factors and fibrinogen. Fibrinolysis is stimulated leading to accumulation of fibrin degradation products.

Management of DIC includes:

- Treatment of the underlying cause
- Platelet transfusion
- Transfusion of FFP; cryoprecipitate may be used instead if fibrinogen is low

## 11.4 Haemophilia A

- Almost 40% of cases present in the neonatal period with IVH, cephalohaematoma or excessive bleeding elsewhere
- Antenatal diagnosis is possible by chorionic villous biopsy, if there is a family history
- Vaginal birth is safe if uncomplicated but Ventouse delivery should be avoided
- Oral vitamin K (rather than intramuscular) should be given
- Bleeding should be treated with recombinant factor VIII, but prophylactic treatment is controversial

Clinical features of haemophilia B in neonates are similar to those of haemophilia A.

## 11.5 Von Willebrand disease

- Two forms of von Willebrand disease may present in neonates
- Type 2b is autosomal dominant, presents with thrombocytopenia but rarely presents with bleeding
- Type 3 is autosomal recessive; presentation is similar to haemophilia A, but girls can be affected

## 12. NEONATAL ORTHOPAEDIC PROBLEMS

See Chapter 21, Section 6.1.

## 13. FURTHER READING

American Academy of Pediatrics Committee on Drugs (1998). Neonatal drug withdrawal. *Pediatrics* **101**:1079–88.

Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR (2000). The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics* **106**:659–71.

Findlay RD, Taeusch HW, Walther FJ (1996). Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics* **97**:48–52.

Greenough A, Milner AD, eds (2003). *Neonatal Respiratory Disorders*, 2nd edn. London: Arnold.

Lucas A, Cole TJ (1990). Breast milk and neonatal necrotising enterocolitis. *Lancet* **336**:1519–23.

Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF (1990). Early diet of preterm infants and

development of allergic or atopic disease: randomised prospective study. *BMJ* 300:837–40.

Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C (1992). Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* 339: 261–4.

Nuffield Council on Bioethics (2006). Critical care decisions in fetal and neonatal medicine: Ethical issues. London: NCB.

Polin RA, Fox WW, Abman SH, eds (2011). *Fetal and Neonatal Physiology*, 4th edn. London: Elsevier.

Rennie JM, ed. (2005). *Roberton's Textbook of Neonatology*, 4th edn, London: Elsevier.

Sweet DG, Carnielli V, Griesen G, et al. (2010). European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2010 update. *Neonatology* 97:402–17.

UK Collaborative ECMO Trial Group (1996). UK Collaborative randomised trial of neonatal ECMO. *Lancet* 348:75–82.

Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR (2000). EPICure Study Group. Neurologic and developmental disability after extremely preterm birth [see comments]. *N Engl J Med* 343:378–84.

## Websites

[www.epicure.ac.uk](http://www.epicure.ac.uk) (Outcome after extremely preterm birth 1995 and 2006)

[www.nuffieldbioethics.org](http://www.nuffieldbioethics.org) (Ethical issues 2006)

[www.nice.org.uk](http://www.nice.org.uk) (Neonatal jaundice, Clinical Guideline 2010)

[www.thecochranelibrary.com](http://www.thecochranelibrary.com) (Cooling for newborns with hypoxic-ischaemic encephalopathy 2008)

[www.thecochranelibrary.com](http://www.thecochranelibrary.com) (Volume targeted versus pressure-limited ventilation in the neonate 2010)

[www.thecochranelibrary.com](http://www.thecochranelibrary.com) (Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants 2009)

[www.thecochranelibrary.com](http://www.thecochranelibrary.com) (Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants 2010)



---

# Chapter 18

## Nephrology

*Christopher J D Reid*

---

## CONTENTS

### 1. Embryology

### 2. Fetal and neonatal renal function

### 3. Physiology

- 3.1 Glomerular filtration rate
- 3.2 Renal tubular physiology
- 3.3 Renin–angiotensin–aldosterone system
- 3.4 Erythropoietin system
- 3.5 Vitamin D metabolism

### 4. Investigations

- 4.1 Urinalysis
- 4.2 Urine microscopy
- 4.3 Haematuria
- 4.4 Proteinuria
- 4.5 Renal imaging
- 4.6 Renal biopsy

### 5. Congenital and urological abnormalities

- 5.1 Hydronephrosis
- 5.2 Duplex kidney
- 5.3 Multicystic dysplastic kidney
- 5.4 Polycystic kidneys
- 5.5 Horseshoe kidney
- 5.6 Hypospadias
- 5.7 Impalpable testes

[5.8 Acute scrotal pain](#)

[5.9 Bladder extrophy and epispadias](#)

## **[6. Acid–base, fluid and electrolytes](#)**

[6.1 Metabolic acidosis](#)

[6.2 Metabolic alkalosis](#)

[6.3 Body fluid compartments and regulation](#)

[6.4 Electrolyte disturbances](#)

## **[7. Renal tubulopathies](#)**

[7.1 Proximal tubulopathies](#)

[7.2 Loop of Henle](#)

[7.3 Distal tubule](#)

[7.4 Collecting duct](#)

## **[8. Nephrotic syndrome](#)**

[8.1 Definitions](#)

[8.2 Clinical features](#)

[8.3 Complications](#)

[8.4 Treatment](#)

[8.5 Congenital nephrotic syndrome](#)

## **[9. Glomerulonephritis](#)**

[9.1 General clinical features](#)

[9.2 Acute post-streptococcal glomerulonephritis](#)

[9.3 Henoch–Schönlein nephritis](#)

[9.4 IgA nephropathy](#)

[9.5 Systemic lupus erythematosus nephritis](#)

[9.6 ‘Shunt’ nephritis](#)

## **[10. Acute kidney injury](#)**

[10.1 Classification of acute kidney injury](#)

[10.2 Differentiating prerenal and intrinsic renal failure/acute kidney injury](#)

[10.3 Initial assessment of acute kidney injury](#)

[10.4 Initial management of child with acute kidney injury](#)

[10.5 Indications for acute dialysis](#)

[10.6 Haemolytic–uraemic syndrome](#)

## **[11. Chronic kidney disease, dialysis and transplantation](#)**

[11.1 Main causes](#)

[11.2 Clinical presentations](#)

[11.3 Main clinical features](#)

[11.4 Dialysis](#)

[11.5 Transplantation](#)

## **12. Urinary tract infection, neuropathic bladder**

[12.1 Urinary tract infection](#)

[12.2 Neuropathic bladder](#)

## **13. Nocturnal enuresis**

[13.1 Definitions](#)

[13.2 Aetiology](#)

[13.3 Assessment](#)

[13.4 Treatment](#)

## **14. Hypertension**

[14.1 Ambulatory blood pressure monitoring](#)

[14.2 Causes of secondary hypertension](#)

[14.3 Evaluation of hypertension by increasing level of invasiveness](#)

[14.4 Treatment of hypertension](#)

## **15. Inherited diseases**

[15.1 Polycystic kidney disease](#)

[15.2 Alport syndrome](#)

[15.3 Nephronophthisis](#)

## **16. Nephrocalcinosis and nephrolithiasis**

[16.1 Nephrocalcinosis](#)

[16.2 Nephrolithiasis-stones](#)

## **17. Further reading**

---

# Nephrology

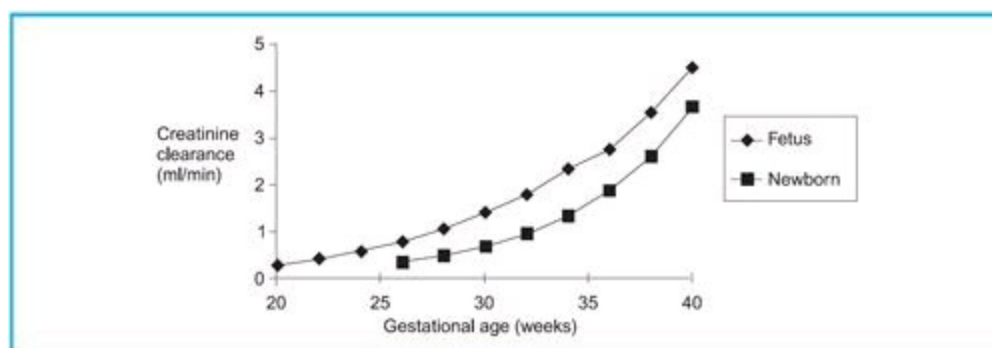
---

## 1. EMBRYOLOGY

- At the start of week 5 of embryogenesis, the ureteric bud appears
- A small branch of the mesonephric duct evolves into a tubular structure which elongates into the primitive mesenchyme of the nephrogenic ridge
- Ureteric bud forms the ureter, and from week 6 onwards repeated branching gives rise to the calyces, papillary ducts and collecting tubules by week 12
- The branching elements also induce the mesenchyme to develop into nephrons – proximal and distal tubules, and glomeruli
- Branching and new nephron induction continues until week 36
- Abnormalities in the signalling between branching ureteric bud elements and the primitive mesenchyme probably underlie important renal malformations including renal dysplasia
- There are on average 600 000 nephrons per kidney. Premature birth and low weight for gestational age may both be associated with reduced nephron numbers
- This, in turn, may underlie the later development of glomerular hyperfiltration, glomerular sclerosis and hypertension, and may explain the firmly established inverse association between birthweight and later adult-onset cardiovascular morbidity

## 2. FETAL AND NEONATAL RENAL FUNCTION

The placenta receives 50% of fetal cardiac output and the fetal kidneys only 5% of cardiac output. By 36 weeks' gestational age nephrogenesis is complete, but glomerular filtration rate (GFR) is <5% of the adult value.



Creatinine clearance (ml/min) in the human fetus and newborn infant.

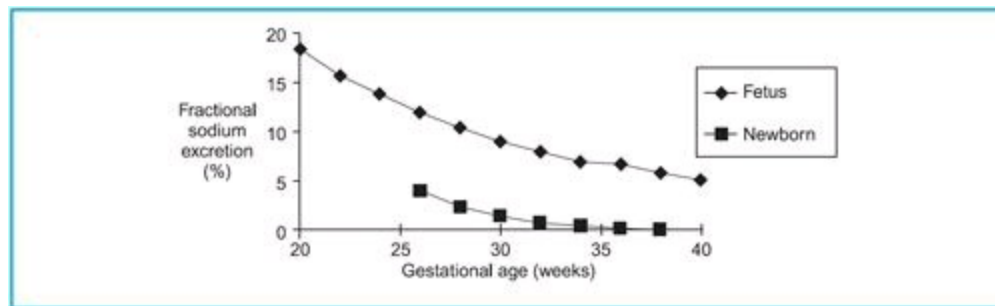
The GFR of term infants at birth is approximately 25 ml/min per 1.73 m<sup>2</sup>, increasing by 50–100% during the first week, followed by a more gradual increase to adult values by the second year of life.

Fractional excretion of sodium (FENa) is:

$$\frac{\text{Urine Na (mmol/l)}}{\text{Urine creatinine (}\mu\text{mol/l)}} \times \frac{\text{Plasma creatinine (}\mu\text{mol/l)}}{\text{Plasma Na (mmol/l)}} \times 100\%$$

- Normal FENa in older children and adults is around 1% and <1% in sodium- and water-deprived states
- It is very high in the premature fetus, falling with increasing gestation, and it is significantly lower in the newborn (see figure below), as the kidney adapts to the demands of extrauterine life where renal tubular conservation of sodium and water is important

Premature neonates still have a relatively high FENa because of immature renal tubular function and require extra sodium supplementation to avoid hyponatraemia.



Fractional sodium excretion (%) in the human fetus and newborn infant.

- Urine-concentrating capacity is low in the premature newborn and leads to susceptibility to dehydration. Fully mature urine-concentrating capacity is reached later in the first year of life
- The plasma bicarbonate concentration at which filtered bicarbonate appears in the urine (bicarbonate threshold) is low in the newborn (19–21 mmol/l), increasing to mature values of 24–26 mmol/l by 4 years. Hence plasma bicarbonate values are lower in infants

Abnormalities in fetal renal function and morphology are mainly inferred from:

- Volume of amniotic fluid – urinary tract obstruction and/or reduced production of urine by dysplastic kidneys lead to oligohydramnios or anhydramnios
- Appearance of kidneys on antenatal ultrasonography – bright echogenicity, lack of corticomedullary differentiation, cyst formation and hydronephrosis are all signs of fetal renal abnormality

Invasive assessment of fetal renal function includes sampling of fetal urine by fine-needle aspiration from the fetal bladder.

- Usually reserved for selected cases of fetal obstructive uropathy, classically caused by posterior urethral valves in male fetuses
- Analysis of fetal urinary electrolytes and amino acid composition may give further information

about fetal renal function and prognosis for postnatal renal function

- Typical features of poor prognosis for renal function (in addition to oligohydramnios and abnormal ultrasound appearance as detailed above) include high urinary sodium and amino acid levels (implying tubular damage and failure to reabsorb these)
- Severe oligohydramnios may lead to pulmonary hypoplasia. This is the major determinant of whether newborns with congenital renal abnormalities live or die in the immediate postnatal period

### 3. PHYSIOLOGY

#### 3.1 Glomerular filtration rate

GFR is determined by:

- The transcapillary hydrostatic pressure gradient across the glomerular capillary bed ( $\Delta P$ ) favouring glomerular filtration
- The transcapillary oncotic pressure gradient ( $\Delta \pi$ ) countering glomerular filtration
- The permeability coefficient of the glomerular capillary wall,  $k$

Hence  $GFR = k(\Delta P - \Delta \pi)$ .

GFR is expressed as a function of body surface area. Absolute values for GFR in millilitres per minute are corrected for surface area by the formula:

Corrected GFR (ml/min/1.73 m<sup>2</sup>)

= Absolute GFR (ml/min)  $\times$  1.73/Surface area

1.73 m<sup>2</sup> is the surface area of an average adult male. Normal mature GFR values are 80–120 ml/min per 1.73 m<sup>2</sup>, and are reached during the second year of life.

GFR can be estimated or measured.

It is **estimated from a calculated value** using the Schwartz formula:

$$\frac{\text{Height (cm)}}{\text{Plasma creatinine } (\mu\text{mol/l})} \times 42 \text{ ml/min per } 1.73 \text{ m}^2$$

This method will tend to overestimate GFR in malnourished children with poor muscle mass.

It is **measured** on a single injection plasma disappearance curve, using inulin, or a radio-isotope such as chromium-labelled EDTA. After an intravenous injection of a known amount of one of these

substances, a series of timed blood samples is taken over 3–5 h, and the slope of the curve generated by the falling plasma levels of the substance gives the GFR. This technique does not require any urine collection, thus making it suitable for routine clinical use.

## 3.2 Renal tubular physiology

The renal tubules play a fundamental role in:

- Maintaining extracellular fluid volume
- Maintaining electrolyte and acid–base homeostasis

These processes are energy demanding and render tubular cells most vulnerable to ischaemic damage and acute tubular necrosis. The proximal tubule and loop of Henle are the sites of major reabsorption of most of the glomerular filtrate.

The distal tubule and collecting duct are where ‘fine tuning’ of the final composition of the urine occurs.

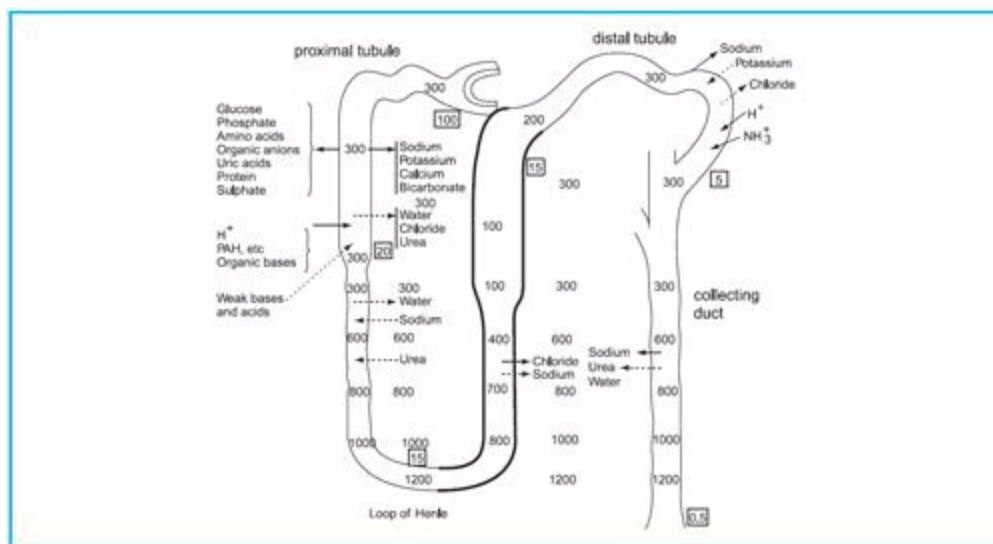


Diagram of tubular function, showing sites of active (solid arrows) and passive (broken arrows) transport. The boxed numbers indicate the percentage of glomerular filtrate remaining in the tubule and the non-boxed numbers the osmolality of the tubular fluid under conditions of antidiuresis. (Reproduced from Godfrey and Baum, *Clinical Paediatric Physiology*, p. 368, Cambridge: Blackwell Scientific Publications, with permission.)

### Proximal tubule

The primary active transport system is the Na<sup>+</sup>/K<sup>+</sup> ATPase enzyme, reabsorbing 50% of filtered Na<sup>+</sup>. Secondary transport involves coupling to the Na<sup>+</sup>/H<sup>+</sup> antiporter, which accounts for 90% of bicarbonate reabsorption with some Cl<sup>-</sup>. In addition:

- Glucose is completely reabsorbed unless the plasma level is high, in which case glycosuria will occur

- Amino acids are completely reabsorbed, although preterm and term neonates commonly show a transient aminoaciduria
- Phosphate is 80–90% reabsorbed under the influence of parathyroid hormone (PTH), which reduces reabsorption and enhances excretion of phosphate
- Calcium is 95% reabsorbed: 60% in the proximal tubule, 20% in the loop of Henle, 10% in the distal tubule and 5% in the collecting duct
- A variety of organic solutes, including creatinine and urate, and some drugs, including trimethoprim and most diuretics, are secreted in the proximal tubule

## Loop of Henle

- A further 40% of filtered  $\text{Na}^+$  is reabsorbed via the  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  co-transporter in the thick ascending limb of the loop of Henle
- The medullary concentration gradient is generated here because this segment is impermeable to water
- Loop diuretics block  $\text{Cl}^-$ -binding sites on the co-transporter
- There is an inborn defect in  $\text{Cl}^-$  reabsorption at this same site in Bartter syndrome – see [Section 7.2](#)

## Distal tubule

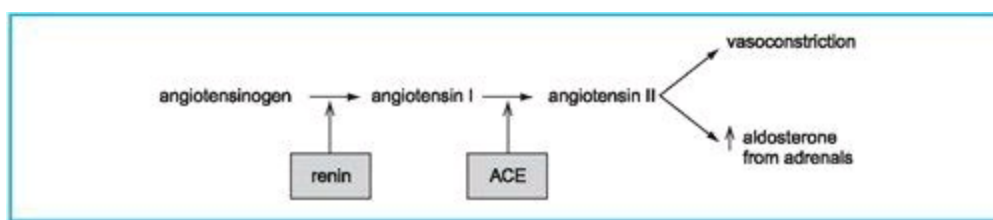
- A further 5% of filtered  $\text{Na}^+$  is reabsorbed here, via a  $\text{Na}^+/\text{Cl}^-$  co-transporter
- Thiazide diuretics compete for these  $\text{Cl}^-$ -binding sites and may have a powerful effect if combined with loop diuretics, which increase  $\text{NaCl}$  and water to the distal tubule
- Aldosterone-sensitive channels (also present in the collecting duct) are involved in regulating  $\text{K}^+$  secretion.  $\text{K}^+$  secretion is proportional to:
  - distal tubular urine flow rate
  - distal tubular  $\text{Na}^+$  delivery: so natriuresis is associated with increased  $\text{K}^+$  secretion and hypokalaemia (e.g. Bartter syndrome, loop diuretics)
  - aldosterone level – so conditions of elevated aldosterone are associated with hypokalaemia
  - $[\text{pH}]^{-1}$

## Collecting duct

- A final 2% of filtered  $\text{Na}^+$  is reabsorbed via aldosterone-sensitive  $\text{Na}^+$  channels, in exchange for  $\text{K}^+$
- Spironolactone binds to and blocks the aldosterone receptor, explaining its diuretic and  $\text{K}^+$ -sparing actions
- $\text{H}^+$  secreted into urine by  $\text{H}^+$  ATPase
- Antidiuretic hormone (ADH) opens water channels (aquaporins) to increase water reabsorption

## 3.3 Renin–angiotensin–aldosterone system





The renin–angiotensin–aldosterone system (ACE, acetylcholinesterase).

- Renin is released from the juxtaglomerular apparatus in response to decreased perfusion to the kidney, leading to increased angiotensin II levels causing vasoconstriction, and increased aldosterone release causing enhanced distal tubular sodium and water conservation, and hence extracellular fluid (ECF) volume expansion
- Abnormal renin release resulting in hypertension is associated with most forms of secondary renal hypertension, e.g. reflux nephropathy and renal artery stenosis

There are syndromes of **low-renin hypertension**, including:

- Conn syndrome – primary hyperaldosteronism: high aldosterone leading to ECF volume expansion, hypertension, hypokalaemia and renin suppression
- Liddle syndrome – constitutive activation of amiloride-sensitive distal tubular epithelial sodium channel: ECF volume expansion leading to renin and aldosterone suppression, and hypokalaemia

**Pseudohypoaldosteronism** is constitutive inactivation of the amiloride-sensitive distal tubular epithelial  $\text{Na}^+$  channel, leading to excessive loss of salt and water with ECF volume depletion, and hyperkalaemia, thus mimicking aldosterone deficiency; renin and aldosterone levels are, however, high secondary to the ECF volume depletion. There are transient and permanent forms.

### 3.4 Erythropoietin system

- Erythropoietin (EPO) is released by renal peritubular cells and stimulates marrow erythropoiesis
- Deficiency of EPO in renal disease is a major cause of the associated anaemia
- Recombinant human EPO is available for treatment and prevention of anaemia in renal failure

### 3.5 Vitamin D metabolism

- Vitamin  $\text{D}_3$  (cholecalciferol) is mainly available from the action of ultraviolet light on its precursor in the skin
- In the liver it is hydroxylated to  $25(\text{OH})$ -vitamin  $\text{D}_3$
- Renal 1-hydroxylase then leads to the production of  $1,25(\text{OH})_2$ -vitamin  $\text{D}_3$ , or calcitriol, the most biologically active vitamin D metabolite, in the kidney
- Hypocalcaemia leads to enhanced 1-hydroxylase activity both directly and indirectly, by stimulating PTH secretion, which also stimulates the enzyme. Other stimuli for increased 1-hydroxylase activity include low serum phosphate and growth hormone

- Deficiency of renal production of calcitriol underlies the rickets of renal failure

## 4. INVESTIGATIONS

### 4.1 Urinalysis

Dipstick testing of urine is routinely used to detect blood, protein, glucose and pH. Multistix can, in addition, detect **leukocyte esterase** (a marker of the presence of polymorphs) and **nitrite** (produced by the bacterial reduction of nitrate). If the urine appears clear to the naked eye and all panels on a Multistix are negative, urine infection is almost certainly excluded. **Note** that urinary haemoglobin and myoglobin (from rhabdomyolysis) produce a false-positive dipstick test for blood; microscopy of urine will not, however, reveal red blood cells.

### 4.2 Urine microscopy

A routine investigation for a urinary tract infection (UTI) and in patients with dipstick haematuria. The finding of organisms and white blood cells on microscopy is strong supporting evidence for the presence of a UTI, before a culture result is available. Apart from infection, the major causes of haematuria in children are glomerular, rather than lower urinary tract. Glomerular red blood cells appear deformed or dysmorphic when examined by an experienced microscopist, helping to localize the site of haematuria to the kidneys.

Urinary casts usually signify renal pathology:

- Red cell casts – isolated renal haematuria or glomerulonephritis
- Tubular cell casts – acute tubular necrosis
- White blood cell casts – pyelonephritis, acute tubular necrosis

### 4.3 Haematuria

The main causes are:

- UTI – bacterial – or other infections including tuberculosis and schistosomiasis
- Glomerulonephritis:
  - Often with proteinuria and urinary casts
  - Isolated haematuria with no other evidence of clinical renal disease may be the presenting feature of several important glomerulonephritides, including Alport syndrome and immunoglobulin A (IgA) nephropathy
- Trauma – usually a history
- Stones – usually painful
- Tumour

- Cystic kidney disease
- Bleeding disorders
- Vascular disorders, including renal vein thrombosis (especially neonates) and arteritis
- Sickle cell disease
- False positives – see [Section 4.1](#)

Factitious – Munchausen syndrome or Munchausen syndrome by proxy Other causes of red urine include beetroot consumption, haemoglobinuria and rifampicin.

## 4.4 Proteinuria

This is usually detected on dipstick testing. The minimum detectable concentration is 10–15 mg/dl, so in a patient producing a large volume of dilute urine the sticks may be negative even though the total amount of protein excreted per day may be significant.

In normal afebrile children, urine protein excretion should not exceed 60 mg/m<sup>2</sup> per 24 h. Collection of an accurate 24-h urine collection is difficult in small children. Quantification of proteinuria is best done on a spot early morning urine sample by measuring urinary albumin (mg/l) and creatinine (mmol/l), and deriving the albumin:creatinine ratio:

- Normal – <3 mg/mmol
- Microalbuminuria – 3–30 mg/mmol
- Proteinuria – >30 mg/mmol

**Orthostatic proteinuria** is detectable when the patient has been in an upright position for several hours but not when the patient is recumbent. It is important to assess protein excretion on a first morning sample, when the patient has been recumbent all night, and on an evening sample when the patient has been up and about all day, because orthostatic proteinuria is a benign condition with a good prognosis, and does not warrant investigations such as renal biopsy.

## 4.5 Renal imaging

### Ultrasonography

This is a readily available non-invasive investigation that is operator dependent for its interpretation. It is the standard for antenatal investigation and in almost all renal conditions.

It gives good information about the following:

- Size, shape, symmetry and position of kidneys
- Hydronephrosis, ureteric dilatation
- Bladder distension, bladder emptying post-void, bladder wall thickness

- Stones – although small ureteric stones may not be seen
- Cystic disease, including autosomal dominant and recessive
- Tumours, including renal and adrenal tumours
- Gross cortical scarring
- Vascular perfusion using a Doppler technique

Ultrasonography may not detect minor degrees of scarring. It is not sensitive or specific at detecting vesicoureteric reflux (VUR). Doppler ultrasonography may reveal renal artery stenosis, but there is a significant false-negative rate.

## **Micturating cystourethrogram (MCUG)**

Used to look for VUR and the appearance of the bladder outline and also the urethra, specifically posterior urethral valves in males.

## **Nuclear medicine isotope scans**

- DMSA (dimercaptosuccinic acid)
- A static scan, i.e. isotope is filtered and retained in renal parenchyma
- Assesses divided function and detects cortical scars
- Main use is in investigation of UTI and hypertension
- Some perfusion defects seen when DMSA is performed during acute UTI may resolve; defects present 3 months after acute infection are permanent

## **MAG-3 (mercaptoacetyltriglycine), DTPA (diethylenetriaminepenta-acetic acid)**

- Dynamic scans, i.e. isotope is filtered, and then excreted from kidney down ureters to bladder
- Assess divided function, and drainage and obstruction
- Main use is in investigating upper tract dilatation seen on ultrasonography and for follow-up of surgery for obstructed kidneys or ureters
- Indirect radioisotope reflux study is a convenient way of assessing the presence of VUR in children old enough to cooperate with the scan and void on demand during the scan – in practice >3 years old. It avoids the need for a urethral catheter and has a lower radiation dose than MCUG

## **Magnetic resonance urography (MRU)**

- Assesses anatomy of urinary tract when the combination of ultrasonography and nuclear medicine scans, and often MCUG, have not clarified issues such as ureteric course and insertion
- Increasingly commonly used for diagnosis and surgical planning of complex urological disorders

## **Intravenous urography**

- Little used now because the combination of ultrasound and isotope scans, and MRU, provides the required information in most cases, and avoids the risks of anaphylaxis and radiation dose that are

involved with intravenous urography (IVU)

- Occasionally used for emergency evaluation of painful haematuria, if ultrasonography is uninformative, when IVU may reveal a ureteric stone

## **Renal arteriography**

- Used to diagnose renal artery stenosis
- Approach is via femoral artery; usually requires general anaesthesia in children.
- Therapeutic approaches include balloon angioplasty of stenoses and embolization of intrarenal arteriovenous aneurysms

## **4.6 Renal biopsy**

In general, the main indications for renal biopsy are:

- to make a diagnosis
- to guide therapy and to assess response to therapy
- to assist in giving a prognosis

The following are the most common reasons for renal biopsy in children:

- Steroid-resistant nephrotic syndrome
- Haematuria and/or proteinuria
- Unexplained acute nephritis/acute renal failure
- Assessment of renal transplant dysfunction

## **5. CONGENITAL AND UROLOGICAL ABNORMALITIES**

### **5.1 Hydronephrosis**

The main causes of hydronephrosis are as follows:

- VUR – see [Section 12.1](#)
- Pelviureteric junction (PUJ) obstruction
  - Usually detected on antenatal ultrasonography
  - Occasionally detected during investigation of UTI or abdominal pain
  - Main aspects of assessment are:
    - ultrasonography – degree of renal pelvic dilatation measured in the anteroposterior diameter: 5–10 mm mild; 11–15 mm moderate; >15 mm severe
    - MAG-3 renogram – findings that suggest significant obstruction are poor drainage despite furosemide given during scan and impaired function, e.g. <40% on hydronephrotic side
    - follow-up in the first 2 years after birth is based around ultrasonography every 4 months, with

MAG-3 scan undertaken if hydronephrosis is severe initially, or progressively worsens over time

- surgical correction is by pyeloplasty
- Usual when MAG-3 indicates obstruction and/or ultrasonography shows progressive increase in hydronephrosis
- When dilatation is  $>30$  mm, surgery is likely
- Surgery is also considered if hydronephrosis is complicated by a proven UTI
- Vesicoureteric junction obstruction
  - Usually detected in the same ways as for PUJ obstruction
  - Ultrasonography shows renal pelvic and ureteric dilatation
  - Interventions include stenting the vesicoureteric junction (temporary measure) and surgical reimplantation

## 5.2 Duplex kidney

- Often detected on antenatal ultrasonography or during investigation of UTI
- Two ureters drain from two separate pelvicalyceal systems; ureters sometimes join before common entry into the bladder, but more commonly have separate entries, with the upper pole ureter inserting below the lower pole ureter
- Common complications associated with duplex systems are:
  - Obstructed hydronephrotic upper moiety and ureter, often poorly functioning, associated with bladder **ureterocele**
    - Dilatation and swelling of submucosal portion of ureter just proximal to stenotic ureteric orifice can be seen within bladder on ultrasonography and as a filling defect on MCUG
  - Ectopically inserted upper pole ureter, entering urethra or vagina; clue to this from history is true continual incontinence with no dry periods at all, as ectopic ureter bypasses bladder
  - VUR into lower pole ureter, sometimes causing infection and scarring of this pole

## 5.3 Multicystic dysplastic kidney

- Irregular cysts of variable size from small to several centimetres; no normal parenchyma
- Dysplastic atretic ureter
- No function on MAG-3 or DMSA scan
- Commonly involute over time
  - No indication for routine surgical removal
  - Follow-up with ultrasonography at 3 months, then 12 months, 2 years and 5 years
- At the 5-year visit, if ultrasonography shows normal contralateral kidney with compensatory hypertrophy of this kidney, and the child has a normal BP, no proteinuria and normal plasma creatinine, then reasonable to discharge from long-term hospital follow-up
- 20–40% incidence of VUR into contralateral normal kidney

## 5.4 Polycystic kidneys

See [Section 15.1](#).

## 5.5 Horseshoe kidney

- Two renal segments fused across midline at lower poles in 95%, upper poles in 5%
- Isthmus usually lies low, at the level of the fourth lumbar vertebra immediately below the origin of the inferior mesenteric artery
- Associations include Turner syndrome, Laurence–Moon–Biedl syndrome
- Usually asymptomatic but increased incidence of PUJ obstruction and VUR, so may develop a UTI

## 5.6 Hypospadias

- Opening of urethral meatus is on the ventral surface of penis, at any point from the glans to base of penis or even perineum
- Meatus may be stenotic and require meatotomy as initial intervention
- Foreskin is absent ventrally; it is used in surgical reconstruction of a deficient urethra so circumcision should not be performed
- Usual best age for surgical correction is around 12 months
- Chordee is the associated ventral curvature of the penis, seen especially during erection, and this also requires surgical correction; caused by fibrous tissue distal to the meatus along the ventral surface of penis

## 5.7 Impalpable testes

- May be intra-abdominal, inguinal or pre-scrotal
- Main aim of diagnosis and management is:
  - to preserve fertility
  - to reduce risk of malignancy and to enable early detection of malignant change if it occurs
- Infants should be referred to paediatric surgeon or urologist by age 6 months
- Ultrasonography may detect inguinal testis, but is of limited use for intra-abdominal testis; MRI may be better, but usually requires general anaesthetic for infant; laparoscopy may be final method for localising testis
- Surgical orchidopexy has 95% success rate; hormonal therapy with human chorionic gonadotrophin (hCG) <15% success and so surgery is preferred option
- Optimum age for surgery is 9–12 months; usually combined with repair of the associated inguinal hernia; may require two-stage procedure for intra-abdominal testis

## 5.8 Acute scrotal pain

- Boys presenting with scrotal pain will often need to be assessed by a paediatric surgeon
- History and examination are the most important components of assessment
- Ultrasonography with colour Doppler to assess testicular blood flow may contribute
- Torsion of testicle:
  - Acute abrupt onset of often severe pain
  - Early puberty
  - Swelling of testis and hemiscrotum, often with erythema/discoloration of scrotal skin
  - Diffuse tenderness of testis
  - Negative urinalysis
  - Treatment is surgical exploration
- Torsion of appendix of epididymis:
  - More common than torsion of testicle
  - Subacute onset of pain over hours
  - Pre-pubertal
  - Tenderness localized to the upper pole of testis
  - Negative urinalysis
  - If confident of diagnosis may be managed conservatively; however, may be difficult to distinguish from torsion of testicle so may require surgical exploration
- Epididymitis:
  - Gradual insidious onset of discomfort or pain
  - Adolescence
  - Epididymal tenderness
  - Urinalysis often positive (although may be negative)
  - May have low-grade fever; raised C-reactive protein (CRP)
  - Treatment with antibiotics (e.g. co-amoxiclav, cefalexin) if urinalysis suggestive of infection
- Trauma:
  - History usually informative
  - Trauma may cause a haematocele or testicular haematoma
- Hernia or hydrocele:
  - Not usually acutely painful
  - Swelling in scrotum, extending into inguinal canal if hernia
  - No erythema or discoloration of overlying scrotal skin
  - Hydrocele will transilluminate with pen torch

## 5.9 Bladder extrophy and epispadias

- Rare disorder; more common in boys
- Bladder mucosa is exposed (and with exposure and infection becomes friable), bladder muscle becomes fibrotic and non-compliant
- Anus anteriorly displaced
- Boys – penis has epispadias (dorsal opening urethra) and dorsal groove on glans, with dorsal chordee and upturning; scrotum is shallow and testes are often undescended
- Girls – female epispadias with bifid clitoris, widely separated labia



- Pubic bones separated
- Requires surgical reconstruction; long-term urinary incontinence is common

## 6. ACID–BASE, FLUID AND ELECTROLYTES

### 6.1 Metabolic acidosis

A primary decrease in plasma bicarbonate and a decrease in plasma pH as a result of:

- Bicarbonate loss, e.g.
  - Gastrointestinal loss in severe diarrhoea
  - Renal loss in proximal (type 2) renal tubular acidosis (RTA)
- Reduced hydrogen ion excretion, e.g.
  - Distal (type 1) RTA
  - Acute and chronic renal failure
- Increased hydrogen ion load, e.g.
  - ↑ endogenous load:
    - inborn errors of metabolism, e.g. maple syrup urine disease, propionic acidaemia
    - lactic acidosis, e.g. cardiovascular shock
    - ketoacidosis, e.g. diabetic ketoacidosis (DKA)
  - ↑ exogenous load, e.g. salicylate poisoning

### Anion gap

- A classification of metabolic acidosis involves assessing the anion gap – the ‘gap’ between anions and cations made up by unmeasured anions, e.g. ketoacids, lactic acid
- Measured as  $[\text{Na}^+ + \text{K}^+] - [\text{HCO}_3^- + \text{Cl}^-]$ ; thus normal anion gap is  $[140 + 4] - [24 + 100] = 20$
- Acidosis may be a normal anion gap, when  $\text{Cl}^-$  will be raised, i.e. hyperchloraemic
- May be an increased anion gap, when  $\text{Cl}^-$  will be normal, i.e. normochloraemic

### Examples:

- Normal anion gap, hyperchloraemia, acidosis – RTA
  - $\text{Na}^+$  140,  $\text{K}^+$  4,  $\text{Cl}^-$  110,  $\text{HCO}_3^-$  14, anion gap = 20
- Increased anion gap, normochloraemia, acidosis – DKA
  - $\text{Na}^+$  140,  $\text{K}^+$  4,  $\text{Cl}^-$  100,  $\text{HCO}_3^-$  15, anion gap = 30

### 6.2 Metabolic alkalosis

A primary increase in plasma bicarbonate and an increase in plasma pH as a result of the following:

- Chloride depletion, the most common cause in childhood, leading to low urinary  $\text{Cl}^-$  and  $\text{Cl}^-$ -responsive alkalosis, i.e. as soon as  $\text{Cl}^-$  is made available (e.g. as intravenous saline) it is retained by the kidney at the expense of  $\text{HCO}_3^-$ , correcting the alkalosis (see also Pseudo-Bartter syndrome, [Section 7.2](#)):
  - Gastrointestinal loss, e.g. pyloric stenosis, congenital chloride diarrhoea
  - Furosemide therapy
  - Cystic fibrosis
- Stimulation of  $\text{H}^+$  secretion by the kidney, with normal urinary  $\text{Cl}^-$  and  $\text{Cl}^-$ -unresponsive alkalosis, e.g.
  - Bartter syndrome (see [Section 7.2](#))
  - Cushing syndrome
  - Hyperaldosteronism (see [Section 3.3](#))
- Excess intake of base, e.g. excess ingestion of antacid medicine (rare in childhood)

## 6.3 Body fluid compartments and regulation

### Total body water

Total body water (TBW) represents 85% of the body weight (bwt) of preterm infants, 80% in term infants and 65% in children. In children it is distributed between the intracellular (ICF) and extracellular (ECF) fluid compartments as follows:

TBW (% bwt)	ICF (% bwt)	ECF (% bwt)	
		Interstitial	Intravascular
65	40	20	5

### Osmotic equilibrium, cell volume regulation

- The major fluid compartments are separated by semipermeable membranes, which are freely permeable to  $\text{H}_2\text{O}$ . Osmotic equilibrium is maintained between the ICF and ECF compartments by the shift of  $\text{H}_2\text{O}$  from lower to higher osmolality compartments
- ECF osmolality can be calculated as:  $[(\text{Na}^+ + \text{K}^+) \times 2] + \text{glucose} + \text{urea}$
- A rise in ECF osmolality, e.g. in DKA, will lead to a shift of  $\text{H}_2\text{O}$  out of the ICF compartment, and thus a reduction in ICF volume, i.e. cell shrinkage. Cell shrinkage stimulates the intracellular accumulation of organic osmolytes, which increases ICF osmolality and leads to a shift of  $\text{H}_2\text{O}$  back into the cell, restoring cell volume
- Treatment of DKA may then lead to the rapid reduction of ECF osmolality, but the ICF organic osmolytes are degraded slowly and thus an osmotic gradient may be created during DKA treatment, favouring movement of  $\text{H}_2\text{O}$  into the cells, causing cerebral oedema

# Osmoregulation

A small (3–4%) increase in ECF osmolality stimulates hypothalamic osmoreceptors to cause posterior pituitary ADH release, leading to water retention and return of osmolality to normal. Increases in ECF osmolality also stimulate thirst and water drinking. Significant (>10%) ECF depletion, **even if iso-osmolar**, will cause carotid and atrial baroreceptors to stimulate ADH release.

## 6.4 Electrolyte disturbances

### Hyponatraemia

Normal plasma  $\text{Na}^+$  is 135–145 mmol/l. Hyponatraemia is usually defined as plasma  $\text{Na}^+ < 130$  mmol/l. The causes are twofold.

#### Gain of $\text{H}_2\text{O}$ in excess of $\text{Na}^+$

- Excess water intake – increased volume of appropriately hypotonic urine:
  - Iatrogenic – excess hypotonic oral or intravenous fluid
  - Psychogenic polydipsia
- Acute renal failure – oedema and hypervolaemia, oliguria with urine  $\text{Na}^+ > 20$  mmol/l
- Syndrome of inappropriate ADH secretion (SIADH) – inappropriately raised urine osmolality, i.e. not maximally dilute; increased body weight; decreased plasma urea and creatinine; absence of overt renal, liver or cardiac disease
  - Meningitis or central nervous system tumour
  - Pneumonia
  - Intermittent positive pressure ventilation
  - Drugs, e.g. carbamazepine, barbiturates
- Treatment is principally water restriction; for severe hyponatraemia ( $< 120$  mmol/l) with neurological symptoms, correction of plasma  $\text{Na}^+$  to 125–130 mmol/l over 4 h is usually safe and effective in correcting symptoms

#### Loss of $\text{Na}^+$ in excess of $\text{H}_2\text{O}$

- Renal losses – dehydration, but inappropriately high urine volume and urine  $\text{Na}^+$  content ( $> 20$  mmol/l); urine isotonic with plasma
  - Loop diuretics
  - Recovery phase of acute tubular necrosis
  - Tubulopathies (see [Section 7.1](#))
  - Salt-wasting congenital adrenal hyperplasia; adrenal insufficiency – hyperkalaemia
- Extrarenal losses – dehydration, appropriate oliguria and  $\text{Na}^+$  conservation with low urine  $\text{Na}^+$  (usually  $< 10$  mmol/l); urine hypertonic

- Gastrointestinal tract losses – gastroenteritis
- Skin losses – severe sweating, cystic fibrosis
- Treatment involves:
  - Rehydration and calculation of  $\text{Na}^+$  deficit as  $(140 - \text{plasma Na}^+) \times 0.65 \text{ body weight (kg)}$
  - Avoid over-rapid correction of hyponatraemia (risk of cerebellopontine myelinolysis)

## Hypernatraemia

Usually defined as plasma  $\text{Na}^+ > 150 \text{ mmol/l}$ . There is a shift of  $\text{H}_2\text{O}$  from the ICF to the ECF compartments, so that, in hypernatraemic dehydration, ECF volume is not markedly reduced and thus typical signs of dehydration are less obvious. The causes are again twofold.

### Loss of $\text{H}_2\text{O}$ in excess of $\text{Na}^+$

- Renal losses – inappropriately high urine output, inappropriately low urine osmolality:
  - Reduced renal concentrating ability – preterm neonates
  - Diabetes insipidus – pituitary and nephrogenic (see [Section 7.4](#))
  - Osmotic diuresis – DKA
- Extrarenal losses – appropriate oliguria and high urine osmolality:
  - Gastrointestinal losses
  - Increased insensible  $\text{H}_2\text{O}$  loss, e.g. pyrexia and hyperventilation
- Inadequate free water intake;
  - Breastfed neonate with inadequate maternal milk flow
- Treatment:
  - Safest and best given with standard oral rehydration solution
  - If intravenous treatment is essential, **slow** (48–72 h or 10–15 mmol/l per 24 h), correction of hypernatraemia with frequent measurement of plasma electrolytes is safest; a suggested fluid is 1 litre dextrose 5% + NaCl 25 mmol + KCl 20 mmol

### Gain of $\text{Na}^+$ in excess of $\text{H}_2\text{O}$

- Increased volume of urine with high  $\text{Na}^+$  content:
  - atrogenic – excess hypertonic intravenous fluid, e.g.  $\text{NaHCO}_3$ , hypertonic saline
  - Incorrect reconstitution of infant formula
  - Accidental or deliberate (e.g. Munchausen syndrome by proxy) salt poisoning
- Treatment – recognition and removal of underlying cause; access to water while kidneys excrete excess salt load

## Hypokalaemia

Normal plasma  $\text{K}^+$  is 3.4–4.8 mmol/l. The following are the main causes of hypokalaemia:

- Inadequate provision of  $K^+$  with prolonged intravenous fluid administration
- Extrarenal losses;
  - Gastrointestinal losses
- Renal losses;
  - High plasma renin levels:
    - diuretic use – loop and thiazide diuretics
    - osmotic diuresis – DKA (hypokalaemia becomes evident when metabolic acidosis and insulin deficiency are corrected)
    - Fanconi syndrome – see [Section 7.1](#)
    - Bartter syndrome – see [Section 7.2](#)
    - Gitelman syndrome – see [Section 7.3](#)
    - distal (type 1) RTA
  - Low plasma renin levels:
    - Conn syndrome – see [Section 3.3](#)
    - Liddle syndrome – see [Section 3.3](#)
    - Cushing syndrome
- Shift from ECF to ICF compartment;
  - Correction of metabolic acidosis
  - Insulin treatment
  - High-dose or prolonged salbutamol treatment for asthma

## Hyperkalaemia

The following are the main causes:

- Excess administration in intravenous fluid
- Renal failure – acute and chronic
- Shift from ICF to ECF;
  - Metabolic acidosis
  - Rhabdomyolysis – acute tumour lysis (both often associated with acute impairment in renal function which compounds the hyperkalaemia)
  - Hypoadrenal states;
    - Salt-wasting congenital adrenal hyperplasia
    - Adrenal insufficiency
    - Pseudohypoaldosteronism – see [Section 3.3](#)
- Potassium-sparing diuretics – spironolactone
- Treatment includes:
  - Exclusion of  $K^+$  from diet and intravenous fluids
  - Cardiac monitor – peaked T waves → prolonged P–R interval → widened QRS ventricular tachycardia → terminal ventricular fibrillation
  - Calcium gluconate to stabilize myocardium
  - Shift  $K^+$  from ECF to ICF:
    - Correct metabolic acidosis if present – in acute renal failure
    - Salbutamol: nebulized or short intravenous infusion

- Insulin and dextrose – but extreme caution in young children as there is a risk of hypoglycaemia
- Remove  $K^+$  from body:
  - calcium resonium
  - dialysis

## Calcium and hypocalcaemia

Calcium in the body is 40% protein bound (of which 98% is bound to albumin), 48% ionized and 12% complexed to anions such as phosphate or citrate

- Normal values are 2.1–2.6 mmol/l for total  $Ca^{2+}$  and 1.14–1.30 for ionized (Io)  $Ca^{2+}$ 
  - Albumin-corrected  $Ca^{2+}$  equals measured total plasma  $Ca^{2+} + [(40 - \text{albumin}) \times 0.02]$  – for example, if total  $Ca^{2+}$  is 1.98 and albumin is 26; corrected  $Ca^{2+} = 1.98 + [(40 - 26) \times 0.02] = 2.26$
- Degree of protein binding of plasma  $Ca^{2+}$  is proportional to plasma pH. Beware of correcting acidosis in renal failure, where total and ionized  $Ca^{2+}$  often already low. Acute rise in pH with  $NaHCO_3$  treatment leads to  $\uparrow$  protein-bound  $Ca^{2+}$  which leads to  $\downarrow$  ionized  $Ca^{2+}$  and may cause tetany
- Monitoring of ionized  $Ca^{2+}$  is useful in intensive care patients, where changes in acid–base and albumin levels make interpretation of total plasma  $Ca^{2+}$  difficult

## Hypocalcaemia

The main symptoms are tetany, paraesthesiae, muscle cramps, stridor and seizures. The main causes are:

- Calcitriol ( $1,25(OH)_2D_3$ ) deficiency;
  - Dietary deficiency of vitamin D
  - Malabsorption of vitamin D – fat malabsorption syndromes
  - Renal failure (acute and chronic) – 1-hydroxylase deficiency
  - Liver disease – 25-hydroxylase deficiency
- Hypoparathyroidism;
  - Transient neonatal
  - DiGeorge syndrome – 22q11.2 deletion
  - Post-parathyroidectomy
- Pseudohypoparathyroidism;
  - Autosomal dominant; end-organ resistance to raised levels of PTH
  - Abnormal phenotype with short stature, obesity, intellectual delay, round face, short neck, shortened fourth and fifth metacarpals
- Acute alkalosis (respiratory or metabolic) or acute correction of acidosis in setting of already reduced  $Ca^{2+}$
- Hyperphosphataemia;
  - Renal failure (acute or chronic)
  - Rhabdomyolysis; tumour lysis syndrome

- Deposition of  $\text{Ca}^{2+}$ ;
  - Acute pancreatitis
- Treatment includes:
  - Intravenous 10% calcium gluconate, 0.2 ml (0.045 mmol)/kg, diluted 1:5 with dextrose 5%, over 10–15 min with ECG monitoring; followed by intravenous infusion of 10% calcium gluconate at 0.3 ml (0.07 mmol)/kg per day
  - Oral  $\text{Ca}^{2+}$  supplements
  - Vitamin D, or the analogue alfacalcidol (1-hydroxycholecalciferol), for nutritional deficiency, hypoparathyroidism and renal failure

## Hypercalcaemia

The main symptoms are constipation, nausea, lethargy and confusion, headache, muscle weakness, and polyuria and dehydration. The main causes are:

- Vitamin D therapy;
  - Renal failure
  - Dietary vitamin D deficiency
- Primary hyperparathyroidism;
  - Neonatal
  - Part of multiple endocrine neoplasia syndromes I and II
- Williams syndrome;
  - Heterozygous deletions of chromosomal sub-band 7q11.23 leading to an elastin gene defect in >90% (detected by fluorescent in situ hybridization [FISH] test)
  - Hypercalcaemia rarely persists beyond 1 year of age
- Familial hypocalciuric hypercalcaemia;
  - Inactivation of  $\text{Ca}^{2+}$ -sensing receptor gene in parathyroid cells and renal tubules leads to an inappropriately high plasma PTH level and inappropriately low urine  $\text{Ca}^{2+}$
- Macrophage production of  $1,25(\text{OH})_2\text{-D}_3$ ;
  - Sarcoidosis
  - Subcutaneous fat necrosis – prolonged or obstructed labour
- Malignant disease;
- Treatment includes:
  - Intravenous hydration plus a loop diuretic
  - Correction/removal or specific treatment of underlying cause, e.g. steroids for sarcoidosis
  - Rarely, bisphosphonates

## Phosphate and hypophosphataemia

Phosphate is excreted from the kidney under the influence of parathyroid hormone (increases excretion) and calcitriol (decreases excretion). In hypophosphataemia, calculation of the **tubular reabsorption of phosphate** (TRP) is useful.

TRP = 1 – Fractional excretion of  $\text{PO}_4^{3-}$

i.e.

$$\text{TRP} = 1 - \left( \frac{\text{Urine } \text{PO}_4^{3-} (\text{mmol/l})}{\text{Urine creatinine } (\mu\text{mol/l})} \times \frac{\text{Plasma creatinine } (\mu\text{mol/l})}{\text{Plasma } \text{PO}_4^{3-} (\text{mmol/l})} \times 100\% \right)$$

Normally, TRP >85%. If the TRP is <85%, in the presence of low plasma  $\text{PO}_4^{3-}$  and a normal PTH level, this implies abnormal tubular leakage of  $\text{PO}_4^{3-}$ .

## Hypophosphataemia

- With appropriately high TRP, i.e. low urinary  $\text{PO}_4^{3-}$ 
  - Dietary  $\text{PO}_4^{3-}$  restriction
  - Increased uptake into bone – the ‘hungry bone syndrome’ seen after parathyroidectomy for prolonged hyperparathyroidism, or after renal transplantation with preceding hyperparathyroidism of chronic renal failure (CRF); see also Hypocalcaemia
- With inappropriately low TRP, i.e. high urinary  $\text{PO}_4^{3-}$ 
  - Hypophosphataemic rickets – see [Section 7.1](#)
  - Fanconi syndrome – see [Section 7.1](#)

## Hyperphosphataemia

- With high urinary  $\text{PO}_4^{3-}$ 
  - Tumour lysis syndrome, rhabdomyolysis – see also Oliguria, Hyperkalaemia
- With low urinary  $\text{PO}_4^{3-}$ 
  - Chronic renal failure – see [Section 11.3](#)
  - Hypoparathyroidism; pseudohypoparathyroidism

## Magnesium and hypomagnasaemia

Most filtered  $\text{Mg}^{2+}$  is reabsorbed in the distal proximal tubule and the loop of Henle. As with  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$  transport and  $\text{NaCl}$  transport are associated. Factors enhancing  $\text{Mg}^{2+}$  reabsorption include hypocalcaemia and raised PTH levels. Hypomagnesaemia is often found in patients with hypocalcaemia and hypokalaemia, and to correct these the magnesium deficiency must also first be corrected. The following are the main causes of hypomagnesaemia:

- Poor dietary intake
- Reduced gut absorption
- Increased urinary losses:
  - Recovery from acute tubular necrosis
  - Post-transplantation diuresis



- Drug induced – loop and thiazide diuretics; amphotericin B; *cis*-platinum
- Gitelman syndrome – see [Section 7.3](#)

## 7. RENAL TUBULOPATHIES

### 7.1 Proximal tubulopathies

#### Cystinuria

- Defect in reabsorption of and hence excessive excretion of, the dibasic amino acids cystine, ornithine, arginine and lysine
- Not to be confused with cystinosis – see below
- Autosomal recessive; two separate cystinuria genes on 2p and 19q
- Cystine is poorly soluble in normal urine pH; it has increased solubility in alkaline urine
- Clinical manifestation is recurrent urinary stone formation
- Stones are extremely hard and densely radio-opaque
- Diagnosis based on stone analysis, or high cystine level in timed urine collection
- Treatment based on high fluid intake ( $>1.5 \text{ l/m}^2$  per day) and alkalization of urine with oral potassium citrate
- If stones still form, oral D-penicillamine leads to formation of highly soluble mixed disulphides with cystine moieties

#### X-linked hypophosphataemic rickets

- Also known as vitamin D-resistant rickets
- Mutation in *PEX* gene on X chromosome
- Isolated defect in  $\text{PO}_4^{3-}$  reabsorption leading to:
  - Inappropriately low tubular reabsorption of  $\text{PO}_4^{3-}$  (TRP) – typically  $<85\%$  – with a normal PTH and calcitriol level
  - Hypophosphataemia
- Earliest sign is  $\uparrow$  alkaline phosphatase (by 3–4 months)
- Plasma  $\text{PO}_4^{3-}$  may be normal until 6–9 months of age
- By 12 months, have delayed growth, hypophosphataemia,  $\uparrow$  alkaline phosphatase and radiological signs of rickets
- Other features include delayed dentition and recurrent dental abscesses
- Treatment is based on calcitriol or alfacalcidol, and phosphate supplements
- Complications of this treatment include hypercalcaemia and nephrocalcinosis
- Recent evidence suggests that addition of growth hormone treatment may improve growth and biochemical disturbance

#### Proximal (type 2) RTA

- Failure to reabsorb filtered  $\text{HCO}_3^-$
- Renal bicarbonate threshold is low, i.e.  $\text{HCO}_3^-$  is present in the urine at levels of plasma  $\text{HCO}_3^-$  lower than normal
- Distal tubular  $\text{H}^+$  excretion is intact so acid urine can be produced
- Normal acidification of urine in response to ammonium chloride load
- Normal increase in urine  $\text{PCO}_2$  in response to 3 mmol/kg oral bicarbonate load
- Ability to excrete acid from distal tubule, and the fact that calcium salts are more soluble in acid urine, is the likely to explain why nephrocalcinosis is not a feature of proximal RTA
- May occur as an isolated defect or as part of Fanconi syndrome – see below
- Symptoms include faltering growth, vomiting and short stature
- Treatment requires large doses of alkali (5–15 mmol/kg per day)

## Fanconi syndrome

- Diffuse proximal tubular dysfunction, leading to excess urinary loss of the following:
  - Glucose – glycosuria with normal blood glucose
  - Phosphate – hypophosphataemia, low TRP, rickets
  - Amino acids – no obvious clinical consequence
  - $\text{HCO}_3^-$  – leading to proximal RTA
  - $\text{K}^+$  – causing hypokalaemia
  - $\text{Na}^+$ ,  $\text{Cl}^-$  and water – leading to polyuria and polydipsia, chronic ECF volume depletion, faltering growth
  - Tubular proteinuria – loss of low-molecular-weight proteins including retinol-binding protein and *N*-acetylglucosaminidase
- Usual clinical features include polyuria and polydipsia, chronic ECF volume depletion, faltering growth, constipation and rickets, with features in addition of any underlying condition

## Main causes of Fanconi syndrome

- Metabolic disorders:
  - Cystinosis
  - Tyrosinaemia
  - Lowe syndrome (oculocerebrorenal syndrome)
  - Galactosaemia
  - Wilson disease
- Heavy metal toxicity
  - Lead, mercury, cadmium
- Idiopathic

## Cystinosis

Autosomal recessive defect in the transport of cystine out of lysosomes. The gene is localized to chromosome 17p and encodes an integral membrane protein, cystinosin.

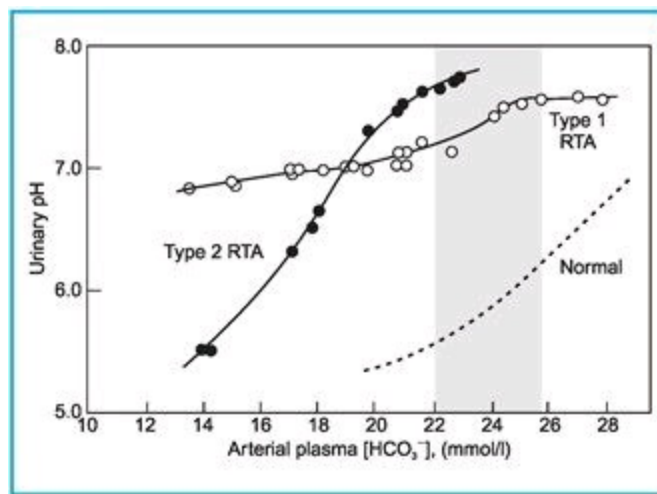
- Predominant early clinical features are of:
  - Fanconi syndrome – see above
  - photophobia as the result of eye involvement with corneal cystine crystals
  - hypothyroidism
- Late features include the following:
  - Renal failure around 8–10 years of age, if untreated
  - Pancreatic involvement with diabetes mellitus
  - Liver involvement with hepatomegaly
  - Gonadal involvement with reduced fertility
  - Neurological deterioration and cerebral atrophy
- Diagnosis is based on the following:
  - Cystine crystals in cornea seen by slit-lamp
  - Peripheral blood white cell cystine level
  - Antenatal diagnosis available for families with positive history

## Treatment

- Supportive –  $\text{PO}_4^{3-}$ , NaCl,  $\text{K}^+$  and  $\text{NaHCO}_3$  supplements, and high fluid intake; alfacalcidol; thyroxine
- Specific – cysteamine, which increases cystine transport out of the lysosome; starting treatment in early infancy appears to delay onset of renal failure
- Other – indometacin reduces the GFR, and hence the severe polyuria and secondary polydipsia, and electrolyte wasting

## Renal tubular acidosis – classification

	Type 1 (distal)	Type 2 (proximal)
Defect	Impaired excretion of $\text{H}^+$	Failure to reabsorb filtered $\text{HCO}_3^-$ ; bicarbonate threshold is low
Urine pH	> 5.8 i.e. never 'acid'	Variable; may be < 5.3
Plasma K	Usually ↓	Normal or ↓
Causes	Primary isolated RTA Nephrocalcinosis Obstructive uropathy Amphotericin; cyclosporin	Primary isolated RTA Transient infantile Fanconi syndrome
Clinical features	Nephrocalcinosis; faltering growth; episodes of severe hypokalaemia	Vomiting; faltering growth; short stature
Response to $\text{NH}_4\text{Cl}$ load	Failure to acidify urine	Production of acid urine
Response to $\text{NaHCO}_3^-$ load	No ↑ in urine–blood $\text{p}(\text{CO}_2)$ gradient	Normal ↑ in urine–blood $\text{p}(\text{CO}_2)$ gradient
Treatment	1–2 mmol/kg/day of $\text{NaHCO}_3$	5–15 mmol/kg/day of $\text{NaHCO}_3$ ; large doses needed to overcome low renal threshold



## Renal tubular acidosis

In normal individuals, urine pH falls as plasma  $HCO_3^-$  decreases through the normal range 26–22 mmol/l. In proximal RTA, the curve has a similar shape but is shifted to the left, such that acid urine is not produced until plasma  $HCO_3^-$  has fallen abnormally low, e.g. 16 mmol/l. In distal RTA, acid urine cannot be produced regardless of how low the plasma  $HCO_3^-$  falls.

## 7.2 Loop of Henle

### Bartter syndrome

- This is caused by an inborn autosomal recessive defect, in the  $Na^+/K^+/2Cl^-$  co-transporter in the thick ascending limb of the loop of Henle, leading to  $NaCl$  and water wasting
- Symptoms are polyuria, polydipsia, episodes of dehydration, faltering growth and constipation; there may be maternal polyhydramnios with an affected fetus
- The resultant ECF volume contraction causes secondary renin secretion and raised aldosterone levels, with avid  $Na^+$  and water reabsorption in the distal tubule, and reciprocal  $K^+$  and  $H^+$  secretion into the urine. (Note that the blood pressure is normal; the hyperreninaemia is a compensatory response to maintain normal blood pressure in the presence of chronic ECF volume depletion.) There is also increased renal prostaglandin  $E_2$  production
- The above changes produce the characteristic biochemical disturbance of hypochloraemic/hypokalaemic alkalosis
- Crucial to the diagnosis is the finding of inappropriately high levels of urinary  $Cl^-$  and  $Na^+$  – usually  $>20$  mmol/l; urine  $Ca^{2+}$  is normal or high (compare Gitelman syndrome – see below)
- Therapy involves  $K^+$  supplementation combined with prostaglandin synthetase inhibitors, usually indometacin

### Pseudo-Bartter syndrome

- The same plasma biochemistry – hypochloraemic hypokalaemic alkalosis – but appropriately low levels of urine  $Cl^-$  and  $Na^+$  –  $<10$  mmol/l

- Main causes are:
  - Cystic fibrosis – sweat loss of NaCl and water
  - Congenital chloride diarrhoea – gastrointestinal loss
  - Laxative abuse – gastrointestinal loss
  - Cyclical vomiting

**Note** that all the changes of Bartter syndrome, including the high urine electrolyte levels, may be produced by loop diuretics, which block the same site in the thick ascending limb of the loop of Henle.

## 7.3 Distal tubule

### Gitelman syndrome

- This condition is considered a variant of Bartter syndrome
- There is an inborn autosomal recessive defect in the distal tubule  $\text{Na}^+/\text{Cl}^-$  co-transporter
- Often asymptomatic, with transient episodes of weakness and tetany with abdominal pain and vomiting
- Patients have hypokalaemic metabolic alkalosis, raised renin and aldosterone, and hypomagnesaemia with increased urinary magnesium wasting, and hypocalciuria, a feature that helps distinguish it from classic Bartter syndrome (in which urinary  $\text{Ca}^{2+}$  is normal or high – see above)
- Biochemical changes resemble those produced by thiazide diuretics, which inhibit this distal tubule co-transporter

## 7.4 Collecting duct

### Nephrogenic diabetes insipidus

- Resistance to action of high circulating levels of ADH
- Associated with ADH-receptor gene mutations (X-linked nephrogenic diabetes insipidus) and aquaporin (water-channel) gene mutations (autosomal recessive nephrogenic diabetes insipidus)
- High volumes of inappropriately dilute urine with tendency to hypernatraemic dehydration

### Liddle syndrome

See [Section 3.3](#).

### Pseudohypoaldosteronism

See [Section 3.3](#).

## 8. NEPHROTIC SYNDROME

A triad of oedema, proteinuria and hypoalbuminaemia. It is almost always idiopathic in childhood. It is best classified by response to steroid treatment – steroid-sensitive nephrotic syndrome (SSNS; 85–90% cases) or steroid-resistant nephrotic syndrome (SRNS; 10–15% cases), because this is the best predictor of outcome.

### 8.1 Definitions

- Remission – negative urinalysis on first morning urine for three consecutive mornings
- Relapse – 3+ proteinuria on three or more consecutive first morning urines
- Frequently relapsing – two or more relapses within 6 months of diagnosis; or four or more relapses per year
- Steroid resistant – no remission after 4 weeks of prednisolone 60 mg/m<sup>2</sup> per day

### 8.2 Clinical features

	SSNS	SRNS
Age at onset	Toddler, pre-school	<1 year; >8 years
Sustained hypertension	No	Often
Microscopic haematuria	Mild, intermittent	Persistent
Renal function	Normal	Often reduced
Long-term prognosis	Excellent, even if frequently relapsing	Poor – significant risk of long-term hypertension and renal failure
Usual histology	Usually not biopsied; from historical data known to be minimal changes	Focal segmental glomerulosclerosis (FSGS)

### 8.3 Complications

#### Infection

- Typically with *Streptococcus pneumoniae*;
  - Pneumonia
  - Primary pneumococcal peritonitis
- Increased risk as a result of:
  - Tissue oedema and pleural and peritoneal fluid
  - Loss of immunoglobulin in urine
  - Immunosuppression with steroid treatment

#### Thrombosis

- Increased risk as a result of:

- Loss of antithrombin III and proteins S and C in urine
- Increased production of procoagulant factors by liver
- Increased haematocrit secondary to reduced oncotic pressure
- Swelling of legs, ascites and relative immobility
- Steroid therapy

## Hypovolaemia

- Reduced plasma oncotic pressure leads to shift of plasma water from intravascular space to interstitial space
- Symptoms include oliguria, abdominal pain, anorexia and postural hypotension
- Signs include cool peripheries, poor capillary refill and tachycardia
- Poor renal perfusion activates the renin–angiotensin–aldosterone system, and urine  $\text{Na}^+$  will therefore be very low – usually  $<10 \text{ mmol/L}$
- Occasionally acute tubular necrosis develops secondary to hypovolaemia

## Drug toxicity

- Most morbidity in childhood nephrotic syndrome arises from side effects of steroid treatment
- Nephrotoxicity from ciclosporin or tacrolimus (see below)

## 8.4 Treatment

### Initial presentation

The most commonly used prednisolone regimen in the UK has been:

- Prednisolone  $60 \text{ mg/m}^2$  per day for 4 weeks; then reduce to  $40 \text{ mg/m}^2$  on alternate days for 4 weeks; then stop

However, there is good evidence from controlled trials that longer duration of initial prednisolone treatment is associated with fewer relapses and lower total prednisolone dose over the first 2 years. An example of a 6-month initial course is:

- $60 \text{ mg/m}^2$  per day for 4 weeks; then  $40 \text{ mg/m}^2$  on alternate days for 4 weeks;  $30 \text{ mg/m}^2$  on alternate days for 4 weeks;  $20 \text{ mg/m}^2$  on alternate days for 4 weeks;  $10 \text{ mg/m}^2$  on alternate days for 4 weeks;  $5 \text{ mg/m}^2$  on alternate days for 4 weeks; then stop

### Relapse

In cases of relapse the most commonly used prednisolone regimen is:

- Prednisolone 60 mg/m<sup>2</sup> per day until in remission; then 40 mg/m<sup>2</sup> on alternate days for three doses; and reduce alternate-day dose by 10 mg/m<sup>2</sup> every three doses until 10 mg/m<sup>2</sup> on alternate days is reached; then 5 mg/m<sup>2</sup> on alternate days for three doses; then stop

## **Frequently relapsing or steroid-dependent nephrotic syndrome**

Other drugs that have been successfully used to enable control without steroids, or with much lower doses of steroids, include:

- Cyclophosphamide:
  - Often used as first choice of second-line drug
  - 2 mg/kg for 12 weeks, or 3 mg/kg for 8 weeks
  - Hair thinning, bone marrow suppression
- Tacrolimus (FK506):
  - Taken twice daily long term, e.g. 12–18 months for initial trial
  - High relapse rate when weaned/stopped
  - Can cause nephrotoxicity – need to monitor plasma tacrolimus levels and GFR
- Ciclosporin:
  - Hirsutism, gum hyperplasia, nephrotoxicity
- Mycophenolate mofetil
  - Most recent immunosuppressive drug tried in nephrotic syndrome
  - Efficacy may be similar to tacrolimus, but not nephrotoxic
  - Gastrointestinal intolerance is the most common side effect
- Levamisole
  - Need to monitor full blood count for bone marrow suppression

## **Steroid-resistant nephrotic syndrome**

- Patient should be referred to specialist renal unit for assessment including renal biopsy
- Usually resistant to other drug treatments also, so full remission not achieved
- Aim is to reduce proteinuria so that patient is no longer nephrotic
- The most common treatment is alternate-day prednisolone combined with ciclosporin long term
- Screen for podocin (*NPHS2*) mutations – patients almost never respond to immunosuppression so can avoid unnecessary drug toxicity
- Angiotensin-converting enzyme (ACE) inhibitor (e.g. enalapril) and/or angiotensin II receptor blocker (e.g. losartan) often used to treat hypertension, with the added benefit of anti-proteinuric effect
- Significant chance of hypertension and progression to renal failure
- If histology is FSGS, associated with 20–40% chance of recurrence after transplantation; however, patients with identifiable podocin or other gene mutations have a much lower risk of disease recurrence

## **8.5 Congenital nephrotic syndrome**



- Onset in first 3 months of life; large placenta – usually 40% of birthweight
- Almost always resistant to drug treatment; clinically severe with high morbidity from protein malnutrition, sepsis
- Main causes are, in decreasing order of frequency:
  - Finnish-type congenital nephrotic syndrome – most severe; autosomal recessive; gene (NPHS1) on chromosome 19 normally codes for nephrin, a cell adhesion protein located at the glomerular slit diaphragm
  - Diffuse mesangial sclerosis – less severe; also autosomal recessive
  - Denys–Drash syndrome – includes pseudohermaphroditism and Wilms tumour
  - FSGS
  - Secondary congenital nephrotic syndrome – congenital syphilis
- Treatment is intense supportive care with 20% albumin infusion, nutritional support and early unilateral nephrectomy (to reduce urinary protein loss), combined with ACE inhibitors and indometacin (to reduce GFR, and thus protein loss, of remaining kidney)
- Eventual progression to renal failure occurs, when remaining kidney is removed, and the child undergoes dialysis and transplantation

## 9. GLOMERULONEPHRITIS

### 9.1 General clinical features

- Inflammation of the glomeruli leading to various clinical features, or renal syndromes, which may include:
  - Haematuria and/or proteinuria
  - Nephrotic syndrome
  - Acute nephritic syndrome with reduced renal function, oliguria and hypertension
  - Rapidly progressive crescentic glomerulonephritis – rapid-onset severe renal failure and hypertension, usually associated with the histological lesion called a crescent
- These renal syndromes are not specific to particular conditions and the same condition may present with different renal syndromes in different patients
- Chronic glomerulonephritis may lead to scarring of the tubulointerstitial areas of the kidney, with progressive renal impairment
- The main causes of glomerulonephritis, and the associated changes in serum complement, include those shown in the table

### The main causes of glomerulonephritis

Normal complement	Reduced complement
Primary renal disease:	Primary renal disease:
FSGS	Acute post-streptococcal GN ↓ C3, normal C4 Mesangiocapillary GN
IgA nephropathy	(MCGN) ↓ C3 and C4

Systemic disease:	Systemic disease:
Henoch-Schönlein nephritis	Systemic lupus erythematosus ↓ C3 and C4 ‘Shunt nephritis’ ↓ C3 and C4

---

GN, glomerulonephritis.

## 9.2 Acute post-streptococcal glomerulonephritis

- Onset of reddish-brown (‘Coca Cola-coloured’) urine 10–14 days after streptococcal throat or skin infection
- May have any of the renal syndromes described above
- Deposition of immune complexes and complement in glomeruli
- Investigations include:
  - Throat swab
  - Antistreptolysin O (ASO) titre; anti-DNAase B
  - Typically ↓ C3, normal C4
  - Biopsy if there is significant renal involvement – diffuse proliferative glomerulonephritis is seen, with crescents, in severe cases
- Treatment is mainly supportive, with an excellent prognosis for recovery; in very severe cases involving renal failure, steroids have been used

**Note:** always check C3 and C4 3 months after acute illness – should normalize; if still lowered there may be another diagnosis, e.g. systemic lupus erythematosus or MCGN, which has much worse prognosis.

## 9.3 Henoch–Schönlein nephritis

- Seventy per cent of children with Henoch–Schönlein purpura will have some degree of renal involvement, usually just microscopic haematuria with/without proteinuria
- They may have any of the renal syndromes described above
- They may have a relapsing course
- Refer to specialist renal unit if nephrotic, or nephritic, or sustained hypertension because these patients may require biopsy
- Prognosis is difficult to be certain about, but initial clinical severity and histological score on biopsy guide the prognosis
- No convincing evidence that treatment with steroids at onset of rash prevents renal involvement (though steroids may be used for systemic symptoms such as abdominal and joint pain)
- Treatment of severe cases includes steroids, ± azathioprine or mycophenolate mofetil (MMF); for very severe crescentic nephritis with renal failure, methylprednisolone combined with intravenous cyclophosphamide and plasma exchange has been used
- Histologically identical to IgA nephropathy – see [Section 9.4](#)
- Follow-up should continue for as long as there continues to be any abnormality on urinalysis
- Accounts for 5–8% of children in end-stage renal failure

## 9.4 IgA nephropathy

- Presents with incidental finding of persistent microscopic haematuria or with an episode of macroscopic haematuria which is typically associated with concurrent upper respiratory infection – these episodes may be recurrent
- Again, may have any of the renal syndromes described above
- Prognosis for childhood presentation is quite good, although 10–15% will develop proteinuria, hypertension with/without renal failure during long-term follow-up
- Treatment as for Henoch–Schönlein purpura nephritis; ACE inhibitors used for long-term control of hypertension and to minimize proteinuria

## 9.5 Systemic lupus erythematosus nephritis

- Again, may present with various renal syndromes
- Histologically variable and the condition may change its clinical and histological features and severity over time
- Treatment of nephritis usually steroids + MMF
- Patients may also manifest the antiphospholipid/anticardiolipin antibody syndrome, with thrombotic complications affecting the renal vasculature

## 9.6 ‘Shunt’ nephritis

- Classically associated with infected ventriculoatrial shunts – these are now rarely used so the condition is rare
- Histologically similar to nephritis of subacute bacterial endocarditis

## 10. ACUTE KIDNEY INJURY

An acute disturbance in fluid and electrolyte homeostasis, typically associated with oliguria (<300 ml/m<sup>2</sup> per day) and retention of urea, potassium, phosphate, H<sup>+</sup> and creatinine. It is rare in childhood compared with the incidence in elderly people. The main cause of severe acute renal failure in otherwise normal children is haemolytic/uraemic syndrome.

### 10.1 Classification of acute kidney injury

#### Prerenal failure with reduced renal perfusion

- In the early stages, the kidney reacts appropriately producing small volumes of urine with very low

Na<sup>+</sup> and high concentration of urea; may be reversible at this stage with fluid therapy (with/without inotropic support)

- If uncorrected, progresses to established acute tubular necrosis
- Main causes are:
  - ECF volume deficiency – haemorrhage, diarrhoea, burns, DKA, septic shock with ‘third-space’ fluid loss
  - Cardiac (‘pump’) failure – congenital heart disease, e.g. severe coarctation, hypoplastic left heart, aortic cross-clamping and bypass for correction of congenital heart disease, myocarditis

## **Intrinsic renal failure**

### **Acute tubular necrosis**

Occurs as a result of:

- Uncorrected prerenal failure as above
- Toxins – gentamicin, X-ray contrast, myoglobinuria; gentamicin toxicity most common in neonates, and may cause non-oliguric renal failure
- Acute glomerulonephritis – see [Section 9](#)

### **Vascular**

- Small vessel occlusion – haemolytic/uraemic syndrome
- Bilateral renal vein thrombosis – neonates
- Acute renal cortical necrosis – neonatal birth asphyxia

### **Tubulointerstitial nephritis**

- Drugs – non-steroidal anti-inflammatory drugs, furosemide, penicillin, cephalosporins

## **Postrenal (obstructive) renal failure**

- Posterior urethral valves is main lesion, but not acute kidney injury
- Neuropathic bladder – may be acute in:
  - Transverse myelitis
  - Spinal trauma or tumour
- Stones:
  - Bilateral pelviureteric junction or ureteral stone or bladder stone
  - Urethral prolapse of bladder ureterocele

## **10.2 Differentiating prerenal oliguria and intrinsic renal failure/acute tubular necrosis**

- Clinical assessment of circulation in oliguric child is crucial:

- Low blood pressure, poor capillary refill and cool peripheries suggest prerenal cause: may respond to fluid challenge
- Normal/raised blood pressure, raised jugular venous pressure (JVP), good peripheral perfusion, gallop rhythm suggest intravascular volume overload and thus not prerenal, and fluid challenge is contraindicated (though challenge with loop diuretic may improve urine output)
- Urine biochemical indices may help

## Urine indices in prerenal and intrinsic renal failure

Urine indices	Prerenal failure	Intrinsic renal failure
Osmolality	>500	<300
Urine Na <sup>+</sup>	<10	>40
Urine:plasma urea ratio	>10:1	<7:1
Fractional excretion of Na <sup>+</sup> (%)	<1	>1

## 10.3 Initial assessment of kidney injury failure

- History may give clues to diagnosis:
  - Sore throat and fever 10 days earlier suggests post-streptococcal glomerulonephritis
  - Bloody diarrhoea and progressive pallor suggest haemolytic/uraemic syndrome
  - Drug history may reveal use of non-steroidal anti-inflammatory drugs (increasingly used for childhood fever, earache, etc.)
- Examination aims to:
  - assess circulation – see [Section 10.2](#)
  - look for clues to diagnosis – drug rash suggests interstitial nephritis; large palpable bladder suggests acute obstructive nephropathy
- Initial investigations:
  - Blood:
    - Electrolytes, chloride, urea, creatinine, phosphate, calcium, magnesium, urate, liver function tests, venous or capillary blood gas
    - Full blood count, blood film (red blood cell fragments in haemolytic/uraemic syndrome)
  - Urine:
    - Urinalysis for blood, protein; glucose (a clue to interstitial nephritis)
    - Urine microscopy for casts
    - Urine Na<sup>+</sup>, urea, creatinine, osmolality – see table above
  - Ultrasonography of urinary tract:
    - With most causes of acute kidney injury, kidneys appear normal or increased in size, with

slightly increased echogenicity (if kidneys appear small with poor corticomedullary differentiation, renal failure is **chronic**)

- Rules out or confirms obstruction of urinary tract; stones
- Can detect clot in renal vein thrombosis

Renal biopsy if diagnosis not clear from above assessment

## 10.4 Initial management of child with acute kidney injury

- Early liaison with paediatric renal unit
- Fluid therapy determined by clinical assessment and urine indices, as above:
  - Prerenal failure: fluid challenge with physiological 0.9% saline
  - Intrinsic renal failure:
    - If clinically euvolaemic, give fluid as insensible loss ( $300 \text{ ml/m}^2$  per day) + urine output
    - If clinically overloaded, challenge with loop diuretic and restrict to insensible losses
- If hypertensive because of ECF volume overload:
  - Challenge with loop diuretic
  - Nifedipine or hydralazine as simple vasodilating hypotensives
- If hyperkalaemic, treat as in Section 6.4

**Note** that if anaemic, e.g. in haemolytic/uraemic syndrome, transfusion usually delayed until dialysis access is established (i.e. until transferred to renal unit), because hyperkalaemia and fluid overload may be worsened

## 10.5 Indications for acute dialysis

- Severe ECF volume overload – severe hypertension, pulmonary oedema, no response to diuretics
- Severe hyperkalaemia, not responding to conservative treatment
- Severe symptomatic uraemia – usually urea  $>40 \text{ mmol/l}$
- Severe metabolic acidosis not controllable with intravenous bicarbonate
- To remove fluid to ‘make space’ for nutrition (intravenous or enteral), intravenous drugs – a common reason in intensive care patients
- Removal of toxins – haemodialysis will be most effective for low-molecular-weight substances that are not highly protein bound, including:
  - Drugs – gentamicin, salicylates, lithium
  - Poisons – ethanol, ethylene glycol
  - Metabolites from inborn errors of metabolism – leucine in maple syrup urine disease, ammonia

## 10.6 Haemolytic–uraemic syndrome (HUS)

- Most common cause of acute kidney injury in children

- Diarrhoea-associated HUS (D<sup>+</sup> HUS) is the major type, usually as the result of *Escherichia coli* O157, which produces verocytotoxin (also called shiga toxin)
- Toxin is released in gut and absorbed, causing endothelial damage especially in renal microvasculature, leading to microangiopathic haemolytic anaemia with thrombocytopenia and red blood cell fragmentation (seen on blood film)
- The microangiopathy leads to patchy focal thrombosis and infarction, and renal failure which is often severe and requires dialysis
- Brain (fits, focal neurology), myocardium, pancreas and liver are sometimes affected
- Treatment is supportive; antibiotic treatment of the *E. coli* gastroenteritis increases the incidence and severity of HUS, and is thus contraindicated
- Long-term follow-up shows that 10–15% will develop hypertension, proteinuria or impaired renal function
- Atypical D<sup>-</sup> HUS is rare but more serious, with recurrent episodes, progressive renal impairment and higher incidence of neurological involvement:
  - Autosomal recessive forms associated with disturbances of complement regulation, e.g. mutations in complement factor H gene
  - Rare complication of bone marrow transplantation

## 11. CHRONIC KIDNEY DISEASE, DIALYSIS AND TRANSPLANTATION

A persistent impairment of renal function, classified according to the GFR as mild (60–80 ml/min per 1.73 m<sup>2</sup>), moderate (40–59 ml/min per 1.73 m<sup>2</sup>) and severe (<40 ml/min per 1.73 m<sup>2</sup>). End-stage renal failure, where dialysis or transplantation is needed, is reached once GFR <10 ml/min per 1.73 m<sup>2</sup>.

### 11.1 Main causes

The main causes are:

- Congenital dysplasia ± obstruction
- Reflux nephropathy
- Chronic glomerulonephritis – FSGS, MCGN
- Genetically inherited disease:
  - Hereditary nephritis – Alport syndrome, nephronophthisis
  - Polycystic kidney disease
- Systemic disease – Henoch–Schönlein purpura, systemic lupus erythematosus

### 11.2 Clinical presentations

- Antenatal diagnosis
- Faltering growth, poor growth, pubertal delay

- Malaise, anorexia
- Anaemia
- Incidental – blood test, urinalysis
- Hypertension

## 11.3 Main clinical features

### Poor growth

- Anorexia, vomiting (uraemia)
- Anaemia, acidosis and renal osteodystrophy – see below
- Reduced effectiveness of growth hormone, probably as the result of raised levels of insulin-like growth factor (IGF)-binding protein, and hence less free IGF; levels of growth hormone are normal
- Recombinant human growth hormone is effective in improving growth in children with chronic renal failure, and is licensed for this use

### Dietary considerations

- Inadequate calorie intake and catabolism worsens acidosis, uraemia and hyperkalaemia in chronic renal failure; aggressive nutritional management is crucial to control these, and to achieve growth
- Children with chronic renal failure often have poor appetite, and infants in particular benefit from nasogastric or gastrostomy tube feeding
- Congenital dysplasia  $\pm$  obstruction typically causes polyuria, with  $\text{NaCl}$  and  $\text{HCO}_3^-$  wasting, and these need supplementing along with generous water intake; note that salt and water restriction is inappropriate in many children with chronic renal failure, until they reach end-stage renal failure
- Protein intake should usually be the recommended daily intake for age; note that protein restriction is inappropriate for children with chronic renal failure
- Dietary restriction of  $\text{PO}_4^{3-}$  (dairy produce) combined with use of  $\text{PO}_4^{3-}$  binders (e.g. calcium carbonate) is essential in controlling secondary hyperparathyroidism
- Dietary restriction of  $\text{K}^+$  (fresh fruits, potatoes) is also commonly needed

### Anaemia

- Dietary iron deficiency
- Reduced red blood cell survival in uraemia
- Erythropoietin deficiency; recombinant human erythropoietin is available for treatment

### Renal osteodystrophy

There are two main contributing processes:

- Phosphate retention leads to hypocalcaemia, and both increased  $\text{PO}_4^{3-}$  and decreased  $\text{Ca}^{2+}$



stimulate secondary hyperparathyroidism:

- Subperiosteal bone resorption

- Deficient renal 1-hydroxylase activity and deficient  $1,25(\text{OH})_2\text{-D}_3$  also contributes to hypocalcaemia, and leads to rickets
- Treatment includes control of hyperphosphataemia (see above) and alfacalcidol (1-OH-cholecalciferol) or calcitriol

## Metabolic acidosis

- Contributes to bone disease, because chronic acidosis is significantly buffered by the uptake of  $\text{H}^+$  into bone in exchange for  $\text{Ca}^{2+}$  loss from bone

## Hypertension

- Depends on the underlying cause of the chronic renal failure
- Congenital dysplasia  $\pm$  obstruction – patients tend to be polyuric, salt wasting and normotensive
- Chronic glomerulonephritis, polycystic kidney disease, systemic disease – hypertension is common; usually secondary to increased renin, so ACE inhibitors are often effective

## 11.4 Dialysis

Once the GFR falls to 10 ml/min per  $1.73 \text{ m}^2$ , the child will usually need dialysis, or transplantation, to be maintained safely. The two main types of dialysis, peritoneal dialysis and haemodialysis, both depend on a semipermeable membrane to achieve solute removal ( $\text{K}^+$ , urea,  $\text{PO}_4^{3-}$ , creatinine, etc.), and fluid removal.

Infants and small children are better suited to peritoneal dialysis, which is more ‘physiological’ and avoids abrupt haemodynamic changes.

	Peritoneal dialysis	Haemodialysis
Semipermeable membrane	Peritoneum membrane	Synthetic membrane
Access	Peritoneal catheter	Central venous catheter or arteriovenous fistula in arm
Frequency and duration	Daily (usually overnight) via automated PD machine	Thrice weekly, 4 h/session
Where	Home	Hospital
Complications	Peritonitis; catheter blockage or leakage	Catheter sepsis; haemodynamic instability in infants
Advantages	Independence from hospital; schooling uninterrupted; PD machine portable so can travel on holidays	No burden of care for dialysis procedure on family
Disadvantages	Burden of care on family	Missed school; travel to and from hospital; limited holiday options

PD, peritoneal dialysis

## 11.5 Transplantation

- The proportion of living related donor transplants in paediatric units (50-70% of transplants) is higher than the national figure overall – a parent is usually the donor
- Transplantation before the need for dialysis is usually the aim
- There are advantages to living related donor transplantation:
  - Better long-term survival of the graft kidney: approximate figures are 95% at 1 year, 80–85% at 5 years, 60% at 10 years
  - Surgery is planned, so family life can be organized to work around this
  - Increases the chance of achieving transplantation without dialysis
- Human leukocyte antigen (HLA) matching is based around HLA-A, -B and -DR; on average a parent and child will be matched for one allele, and mismatched for one allele, at each site
- The main immunosuppressive drugs are prednisolone, tacrolimus and azathioprine
- Children should receive all routine childhood immunisations, and also be immune to tuberculosis, chickenpox and hepatitis B before transplantation
- Children must weigh >10 kg for transplantation to be performed
- The main complications of transplantation include:
  - Early surgical complications – bleeding, transplant artery thrombosis, wound infection
  - Rejection – diagnosed on biopsy; usually treatable with extra immune suppression
  - Opportunistic infection – fungal infections, cytomegalovirus, *Pneumocystis jiroveci* pneumonia
  - Drug toxicity – hypertension, cushingoid changes, hirsutism and nephrotoxicity from ciclosporin
  - Post-transplantation lymphoproliferative disorder – lymphoma-like condition, especially associated with primary Epstein–Barr virus infection when immunosuppressed

## 12. URINARY TRACT INFECTION AND NEUROPATHIC BLADDER

### 12.1 Urinary tract infection

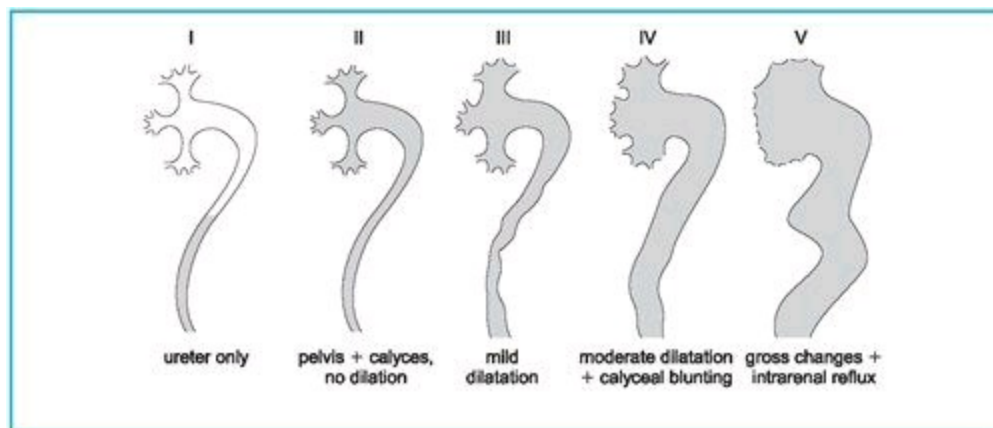
See <http://guidance.nice.org.uk/CG54> for published NICE guideline

- Most common presenting urinary tract problem – 1% boys and 3% girls
- Boys outnumber girls until 6 months (posterior urethral valves); thereafter girls outnumber boys
- Significance of UTI:
  - Renal scar gives 15–20% risk hypertension
  - Reflux nephropathy causes 15–20% end-stage renal failure
- Age at greatest risk for renal damage, age in which symptoms of UTI are least specific, age group most often seen with fever by general practitioners and age at which proper urine samples are hardest to obtain – infancy
- Collection of an uncontaminated urine sample is crucial to accurate diagnosis of UTI – methods include:
  - Clean catch
  - Adhesive bag – problems with leakage and faecal contamination
  - Absorbent pad – also prone to contamination

- Catheter specimen, or suprapubic aspirate – suitable if urine sample is needed urgently, e.g. septic screen in ill infant

## Predisposing factors for UTI

- VUR:
  - Familial, behaves as autosomal dominant condition
  - May be graded according to severity on MCUG
  - Management based on long-term, low-dose antibiotic prophylaxis (although no convincing randomized prospective controlled trials have been reported, this remains the standard of care currently)
  - Significant spontaneous resolution rate; less likely in grades IV and V
  - Controlled studies show no benefit for surgery over conservative management for grades I–III
  - Surgery may be indicated where prophylaxis fails to control infection and where there is progressive reflux nephropathy; options are reimplantation of ureters or endoscopic injection of synthetic material at ureteric orifice
  - Screening of newborn siblings or offspring of index children or parents should be considered
  - In children who have normal bladder control and no symptoms of detrusor dysfunction, and who have been free of infection on prophylaxis, evidence suggests that there is little benefit from continuing prophylaxis beyond age 5 years
- Incomplete bladder emptying:
  - Posterior urethral valves
  - Neuropathic bladder
- Catheterization or instrumentation of urinary tract
- Stones



Grading of vesicoureteric flux

## Classification of UTI (according to NICE Guidelines)

### Atypical UTI

Seriously ill  
Poor urine flow

### Recurrent UTI

Two or more episodes of UTI with acute pyelonephritis/upper urinary tract infection

Abdominal or bladder mass	
Raised creatinine	
Septicaemia	One episode of UTI with acute pyelonephritis/upper urinary tract infection plus one or more episode of UTI with cystitis/lower urinary tract infection
Failure to respond to treatment with suitable antibiotics within 48 hours	
Infection with non- <i>E. coli</i> organisms	Three or more episodes of UTI with cystitis/lower urinary tract infection

## Investigation of UTI (according to NICE Guidelines)

### Aims

- To identify scarring
- To identify underlying abnormalities likely to cause recurrent infection – VUR; incomplete emptying
- There has been much debate about the investigation of UTI but the scheme below follows current NICE Guidelines
- Indirect radioisotope reflux study (e.g. MAG-3) – see [Section 4.5](#) may be used for subsequent follow-up of VUR detected on MCUG during infancy

Investigation	Responds to treatment within 48 h			Atypical UTI			Recurrent UTI		
	<6 months	≥6 months to <3 years	≥3 years	<6 months	≥6 months to <3 years	≥3 years	<6 months	≥6 months to <3 years	≥3 years
Ultrasound scan acutely	No	No	No	Yes	Yes	Yes <sup>c</sup>	Yes	No	No
Ultrasound scan within 6 weeks	Yes <sup>a</sup>	No	No	No	No	No	No	Yes	Yes <sup>c</sup>
DMSA at 4–6 months	No	No	No	Yes	Yes	No	Yes	Yes	Yes
MCUG	No	No	No	Yes	No <sup>b</sup>	No	Yes	No <sup>b</sup>	No

[9](#) [10](#) [11](#) [11](#) [10](#)

## Prevention of UTI

- Non-pharmacological methods:
  - Avoidance of constipation; correct bottom wiping
  - Frequent voiding and high fluid intake; double voiding
  - Lactobacilli in live yoghurt; cranberry juice
  - Clean intermittent catheterization: requires training of carer or child by specialist nurse
- Prophylactic antibiotics

## Treatment of UTI

NICE guidelines recommend use of urgent microscopy and culture for diagnosis of UTI in infants <3 years old; and dipstick testing as initial test for children ≥3 years old:

- If the infant or child is younger than 3 months; treat with parenteral antibiotics
- If the infant or child is 3 months or older with pyelonephritis/upper urinary tract infection:
  - Treat with oral antibiotics for 7–10 days
  - If oral antibiotics cannot be used, use intravenous antibiotics for 2–4 days followed by oral antibiotics for a total duration of 10 days
- If the infant or child is 3 months or older with cystitis/lower UTI:
  - Treat with oral antibiotics for 3 days
  - If the child is still unwell after 24–48 hours they should be reassessed; if no alternative diagnosis, send urine for culture
- >90% childhood UTIs are *E. coli*
- Obstructed kidneys may need drainage
- Bladder catheter if bladder outlet obstruction
- Nephrostomy insertion if PUJ or VUJ level obstruction
- Stones may need removing
- Augmented bladders may improve with mucolytic and bacteriostatic washouts:
  - Parvolex washouts; chlorhexidine washouts

## 12.2 Neuropathic bladder

Important cause of renal damage:

- UTI caused by incomplete emptying
- High-pressure VUR
- Progressive renal scarring

### Causes

- Spina bifida, sacral agenesis (maternal diabetes)
- Tumour, trauma
- Transverse myelitis

### Types

- Hyperreflexic – high pressure, detrusor-sphincter dyssynergia
- Atonic – large, chronically distended, poorly emptying

### Principles of management

- Videourodynamic assessment of type of bladder dysfunction
- Careful assessment of kidney structure, scarring, function, blood pressure
- Improve emptying with clean intermittent catheterization
- Anticholinergics (oxybutinin) may help reduce unstable contractions
- Augmentation cystoplasty – larger capacity, lower pressure

## 13. NOCTURNAL ENURESIS

See <http://guidance.nice.org.uk/CG111> for published NICE guideline

This is a common condition that is benign but which may cause distress and psychological upset to the child and family. Most children become dry at night 6–9 months after becoming dry by day, which is usually by 3 years. As a simple guide, 10% of 5 year olds and 5% of 10 year olds wet the bed at least one night per week. It is more common in boys.

The NICE guideline referred to above has full and detailed information on all aspects of nocturnal enuresis.

### 13.1 Definitions

- Primary nocturnal enuresis (80%) – never achieved night-time dryness
- Secondary nocturnal enuresis – recurrence of bedwetting having been dry for >6 months
- Initial successful response – 14 consecutive dry nights within 16 weeks of starting treatment
- Relapse – more than 2 wet nights in 2 weeks
- Complete success – no relapse within 2 years of initial success

### 13.2 Aetiology

- Rarely an organic cause; should be distinguished from true incontinence, e.g. as a result of neuropathic bladder or ectopic ureter, when child is never dry
- Genetic component:
  - More common where there is a first-degree relative with history of enuresis
  - Concordance in monozygotic twins twice that in dizygotic twins
- No significant excess of major psychological or behavioural disturbance, although family stress, bullying at school, etc. may trigger secondary enuresis and such factors should be sought in the history
- Evidence from studies that:
  - In younger children, bladder capacity is reduced compared with non-enuretic children
  - In older children and adolescents, there is reduction in the normally observed rise in nocturnal ADH levels and in the decrease in nocturnal urine volume (hence rationale for desmopressin [DDAVP] treatment – see [Section 13.4](#))

### 13.3 Assessment

- Careful history is crucial

- Examination should exclude abnormalities of abdomen, spine, lower limb neurology, hypertension
- No routine investigations are indicated, other than urinalysis if the enuresis has started recently or if there are other symptoms suggesting UTI

## 13.4 Treatment

Sustained and frequent support and encouragement for child and parents from an enthusiastic carer (doctor, nurse) is the most essential factor in seeing improvement. Any treatment must involve the child, and depends for success on their motivation.

- Star charts; colouring-in charts – simple behavioural reward therapy that is successful in many children, and should be part of the monitoring of all interventions
- Enuresis alarms:
  - Mat on bed attached to bed-side buzzer
  - Small moisture sensor worn between two layers of underwear with vibrator alarm attached to pyjamas (has the advantage of detecting wet underwear rather than waiting to detect a wet bed)
  - More effective than drug therapies in direct comparative trials
  - Should be mainstay of treatment, but enthusiastic and supportive care, and involvement of child (e.g. they should get up and change bedding) are crucial to success
- Reassess after 4 weeks of use:
  - Continue with alarm if early signs of some response; if 2 weeks of consecutive dry nights, stop alarm; consider alarm use again if enuresis recurs
  - Consider adding desmopressin if no sign of improvement
- Drug therapy:
  - Desmopressin (oral or intranasal) – meta-analysis of all published trials showed relatively poor short-term complete response rate, high relapse rate and poor long-term cure rate; more effective in older children; useful for short-term control for special situations, e.g. school trip; may be combined with alarm
  - Oxybutinin – should be restricted to those children with a clear history of **detrusor instability** – daytime urgency, frequency, urge incontinence – many of whom also wet the bed
  - Imipramine – low long-term success rate; high relapse rate; potentially serious side effects; rarely used

## 14. HYPERTENSION

Most significant hypertension in childhood is secondary to an underlying cause. **Essential hypertension** is a diagnosis of exclusion; the typical patient is an obese adolescent with mild hypertension and a family history of hypertension.

### What is normal?

- Blood pressure rises throughout childhood, related to age and height

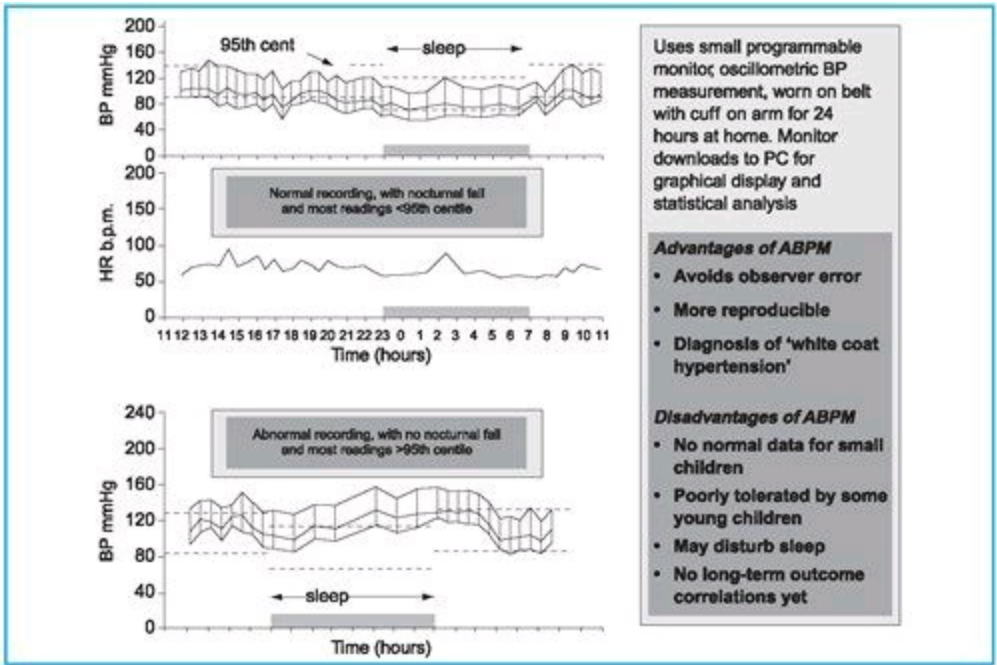


- Depends on method and frequency of measurement
- US Task Force on Blood Pressure Control produced centile charts based on 60 000 normal children and teenagers – see [www.nhlbi.nih.gov/health/prof/heart/hbp/hbp\\_ped.pdf](http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf)

## What is abnormal?

- Consistently above the 95th centile for age
- Loss of normal diurnal pattern
- Infants and toddlers may require admission to hospital for blood pressure monitoring to make diagnosis

## 14.1 Ambulatory blood pressure monitoring



Ambulatory blood pressure monitoring (ABPM).

## 14.2 Causes of secondary hypertension

Cause	Potentially curable by surgery/intervention
<i>Renal</i>	
Reflux nephropathy	If unilateral only
Polycystic kidney disease	✗
Glomerulonephritis, e.g. FSGS	✗
Renal artery stenosis	✓
Middle aortic syndrome, e.g. neurofibromatosis type 1;	✓



Williams syndrome	
Coarctation	✓
<i>Endocrine</i>	
Phaeochromocytoma	✓
Cushing syndrome	✓
<i>Other</i>	Depends on cause

---

### 14.3 Evaluation of hypertension by increasing level of invasiveness

Level 1	Level 2	Level 3
<i>Assessment of risk factors</i> Family history; obesity	<i>Further renal imaging</i> DMSA scan	<i>Arteriography</i> Renal artery stenosis
<i>Consequences of HT</i> Symptom history Fundoscopy Echocardiography	<i>Urine catecholamines</i> 24-h total Catecholamine : creatinine ratio on spot sample	<i>Renal vein renin sampling</i> <i>IVC catecholamine</i> sampling
<i>Secondary renal causes of HT</i> Urinalysis U&E, creatinine, pH Renal ultrasound scan	<i>Further blood samples</i> Renin, aldosterone Plasma catecholamines  <i>Other imaging</i> MIBG scan for phaeo-chromocytoma	<i>Renal biopsy</i>

HT, hypertension

### 14.4 Treatment of hypertension

#### Short-term treatment of acute hypertension

- Most common clinical indication is acute nephritis with salt and water retention; simple and well-tolerated combination would be a loop diuretic, e.g. furosemide, plus a vasodilating  $\text{Ca}^{2+}$ -channel blocker, e.g. nifedipine
- Phaeochromocytoma –  $\alpha$  and  $\beta$  blockers, e.g. phenoxybenzamine + labetolol

#### Urgent treatment of hypertensive encephalopathy

- Severe hypertension with headache, vomiting, hyperreflexia, seizures
- Principle of treatment is:
  - **controllable** reduction with intravenous infusions – labetolol; sodium nitroprusside
  - **gradual** reduction – end-organ damage, e.g. seizures often controlled before normal blood pressure is seen
  - risk of treatment is too rapid reduction causing stroke; cortical blindness

#### Long-term treatment of chronic hypertension

- Aim to use single agent if possible, and select long-acting once-daily agent to aid compliance, e.g.
  - $\beta$  blocker – atenolol
  - $\text{Ca}^{2+}$ -channel blocker – amlodipine
  - ACE inhibitor – enalapril; logical choice for hypertension secondary to chronic renal disease (e.g. reflux nephropathy; FSGS); also has an anti-proteinuric effect; relatively contraindicated in renal artery stenosis

## 15. INHERITED DISEASES

### 15.1 Polycystic kidney disease

#### **Autosomal recessive polycystic kidney disease (ARPKD)**

- Gene is on chromosome 6
- Tubular dilatation of distal collecting ducts, i.e. not true cysts
- Clinical presentation:
  - Antenatal ultrasonography – large echobright kidneys; oligohydramnios
  - At birth or early infancy – large palpable renal masses; respiratory distress secondary to pulmonary hypoplasia
  - At any time – signs and symptoms of chronic renal failure; hypertension – often very severe
- Median age for onset of end-stage renal failure around 12 years, although may cause severe renal failure in infancy; very variable disease severity even within same family
- Always associated with congenital hepatic fibrosis, which may vary from subclinical to causing liver disease – the dominant clinical feature; complications include ascending cholangitis

#### **Autosomal dominant polycystic kidney disease (ADPKD)**

- At least two gene loci; most common on chromosome 16 (adjacent to tuberous sclerosis gene); normal gene product is polycystin
- True cysts arising from tubules – get larger and more numerous with time and hence cause progressive decline in renal function
- An important cause of hypertension and renal failure in adults although may present in childhood
- Clinical presentation – again, very variable in age and severity:
  - Antenatal ultrasonography – discrete cysts in fetal kidneys (**note**; always scan parents' kidneys)
  - Microscopic haematuria
  - Hypertension; renal failure
  - Incidental finding of renal cysts during abdominal ultrasonography – first cysts may not appear until patient is in 20s; may be unilateral
- Associated with cerebral aneurysms and subarachnoid haemorrhage

### 15.2 Alport syndrome

- Hereditary nephritis with sensorineural deafness and anterior lenticonus (conical deformity of lens of eye seen with slit-lamp)
- X-linked (most common) and autosomal recessive forms
  - X-linked – males affected; female carriers all have microscopic haematuria; with lyonization some females may develop hypertension and renal disease, but with milder and later onset
  - Autosomal recessive (chromosome 2) – both sexes equally severe
- Basic defect is in production of subunits for type IV collagen (two subunits coded for on X chromosome, two on chromosome 2); type IV collagen is located in kidney, eye and inner ear – hence the main clinical features
- Presents with incidental finding of microscopic haematuria, or episode of macroscopic haematuria
- Deafness around 10 years
- Hypertension in mid-teens
- Eye signs in mid-late teens (not before 12 years)
- Average age for end-stage renal failure is 21 years

## 15.3 Nephronophthisis

- Autosomal recessive condition; gene (called *NPHP1*) on chromosome 2
- Produces polyuria (concentrating defect), growth delay and often severe anaemia
- Urinalysis typically ‘bland’ – sometimes a trace of glucose
- Progresses to end-stage renal failure towards the end of the first decade
- Sometimes associated with tapetoretinal degeneration: Senior–Løken syndrome

## 16. NEPHROCALCINOSIS AND NEPHROLITHIASIS

### 16.1 Nephrocalcinosis

Diffuse speckling calcification is seen on ultrasound scans or plain radiograph.

The main causes are:

- Distal RTA
- Ex-premature neonates:
  - Furosemide – hypercalciuria
  - Steroids – hypercalciuria
- Vitamin D treatment for hypophosphataemic rickets:
  - Enhances tubular reabsorption of  $\text{Ca}^{2+}$
- Oxalosis:
  - Autosomal recessive disorder
  - Primary hyperoxaluria associated with defect in alanine:glyoxylate aminotransferase (AGT) enzyme, which leads to excess oxalate production and urinary oxalate excretion

- Calcium oxalate precipitates, nephrocalcinosis and obstructing stones form, renal failure ensues
- Systemic oxalosis – joints, heart, blood vessels
- Treatment – liver transplantation alone if renal function only moderately reduced; sequential liver then kidney transplantation if renal failure established, with intense dialysis therapy between the two operations to lower the systemic oxalate burden (simultaneous liver–kidney transplantation presents high risk of oxalate deposition in newly transplanted kidney)

## 16.2 Nephrolithiasis – stones

- Uncommon in paediatrics
- Clinical presentation:
  - Painful haematuria
  - Revealed during investigation into UTI
- Important to undertake metabolic analysis of timed urine collection, or of stone itself if possible, because several metabolic diseases cause stones which may be recurrent

Type	Cause	Radio-opaque
Magnesium ammonium phosphate	Proteus UTI; urinary stasis	±
Calcium phosphate	RTA; hypercalciuria	+
Calcium oxalate	Oxalosis	+
Cystine	Cystinuria	+
Uric acid	Lesch–Nyhan; tumour lysis	–
Xanthine	Xanthinuria	–

RTA, renal tubular acidosis; UTI, urinary tract infection.

## 17. FURTHER READING

Webb, NJ, Postlethwaite RJ, eds (2003). *Clinical Paediatric Nephrology*, 3rd edn. Oxford; Oxford University Press.

---

# Chapter 19

## Neurology

*Neil H Thomas*

---

### **1. Developmental abnormalities of the nervous system**

- [1.1 Normal development of the nervous system](#)
- [1.2 Neural tube defects](#)
- [1.3 Hydrocephalus](#)
- [1.4 Disorders of cortical development](#)
- [1.5 Other nervous system maldevelopments](#)

### **2. Neonatal neurology**

- [2.1 Neonatal seizures](#)
- [2.2 Hypoxic–ischaemic encephalopathy](#)
- [2.3 Periventricular–intraventricular haemorrhage](#)
- [2.4 Periventricular leukomalacia](#)
- [2.5 Brachial plexus injuries](#)

### **3. Disorders of movement**

- [3.1 Cerebral palsy](#)
- [3.2 Ataxia](#)
- [3.3 Dystonia](#)
- [3.4 Tics, Gilles de la Tourette syndrome](#)

### **4. Developmental disabilities**

- [4.1 Learning disability](#)
- [4.2 Autism](#)
- [4.3 Attention-deficit hyperactivity disorder](#)
- [4.4 Deficits in attention, motor control and perception](#)

### **5. Epilepsy**

- [5.1 Diagnosis](#)
- [5.2 Definition and classification](#)
- [5.3 Generalized epilepsies](#)

[5.4 Partial epilepsies](#)

[5.5 Assessment and treatment of epilepsies](#)

[5.6 Anticonvulsant drugs](#)

[5.7 Management of status epilepticus](#)

## **[6. Non-epileptic seizures](#)**

[6.1 Anoxic seizures](#)

[6.2 Psychogenic seizures](#)

## **[7. Headaches](#)**

[7.1 Tension headaches](#)

[7.2 Migraine](#)

[7.3 Other headaches](#)

## **[8. Abnormalities of head size and shape](#)**

[8.1 Macrocephaly](#)

[8.2 Microcephaly](#)

[8.3 Abnormal head shape](#)

## **[9. Neuromuscular disorders](#)**

[9.1 The floppy infant](#)

[9.2 Duchenne muscular dystrophy](#)

[9.3 Becker muscular dystrophy](#)

[9.4 Other muscular dystrophies and congenital myopathies](#)

[9.5 Anterior horn cell disease](#)

[9.6 Neuropathies](#)

[9.7 Acute neuromuscular disorders](#)

[9.8 Disorders of neuromuscular junction](#)

## **[10. Central nervous system infections and parainfectious disorders](#)**

[10.1 Meningitis](#)

[10.2 Encephalitis](#)

[10.3 Immune-mediated disorders](#)

## **[11. Cerebrovascular disease](#)**

[11.1 Arterial occlusion](#)

[11.2 Venous thrombosis](#)

## **[12. Neuro-oncology](#)**

[12.1 Posterior fossa tumours](#)

[12.2 Brain-stem tumours](#)

[12.3 Supratentorial tumours](#)

## **[13. Neurocutaneous disorders](#)**

[13.1 Neurofibromatosis](#)

[13.2 Tuberous sclerosis](#)

[13.2 Other neurocutaneous disorders](#)

## **[14. Neurometabolic diseases](#)**

[14.1 Amino and organic acid disorders](#)

[14.2 Neurotransmitter and urea cycle disorders](#)

[14.3 Mitochondrial disease](#)

[14.4 Abnormalities of copper metabolism](#)

[14.5 Storage disorders](#)

[14.6 Leukodystrophies and other neurodegenerative disorders](#)

## **[15. Head injury](#)**

[15.1 Mild closed head injury](#)

[15.2 Severe closed head injury](#)

[15.3 Non-accidental head injury](#)

## **[16. Specific neurological lesions](#)**

[16.1 Cranial nerve lesions](#)

[16.2 Disorders of eye movement](#)

[16.3 Unequal pupils](#)

## **[17. Neurological investigations](#)**

[17.1 Electroencephalography](#)

[17.2 Evoked potentials](#)

[17.3 Peripheral neurophysiology](#)

[17.4 Brain imaging](#)

[17.5 Lumbar puncture](#)

## **[18. Further reading](#)**

1. DEVELOPMENTAL ABNORMALITIES OF THE NERVOUS SYSTEM

1.1 Normal development of the nervous system

The exact details of the normal development of the nervous system are complex, but the important stages can be summarized in the table below:

Stage	Time	Event	Potential disorder
Organ induction: (a) Dorsal (b) Ventral	3–7 weeks 5–6 weeks	Neural tube closure Forebrain, facial development	Anencephaly, spina bifida Holoprosencephaly
Neuronal and glial proliferation	8–16 weeks	Neural proliferation and early cellular differentiation	Microcephaly
Neuronal migration	12–19 weeks	Neuronal migration and formation of corpus callosum	Lissencephaly, pachygyria, agenesis of corpus callosum
Neuronal organization	22 weeks postnatal	Orientation of cortical structures	Cortical dysplasia
Myelination	24 weeks through early childhood years		Dysmyelination

1.2 Neural tube defects

Spina bifida occulta

Asymptomatic condition characterized by failure of closure of vertebral arch. Occurs in up to 5% of the population.

Anencephaly

Failure of closure of the rostral aspect of the neural tube; 75% of affected infants stillborn.

Encephalocele

Protrusion of cerebral tissue through midline cranial defect located in frontal or occipital regions.



# Meningocele

Cyst formed by herniation of meninges, usually over dorsum of spine. Neurological disability minimal, risk of bacterial meningitis.

# Meningomyelocele

Herniation of meninges, nerve roots and spinal cord through dorsal vertebral defect. Leads to motor and sensory deficits below lesion, including sphincter disturbance. May be associated with other malformations of spinal cord including Arnold–Chiari malformation (downward displacement of cerebellar tonsils through foramen magnum). Hydrocephalus may coexist, secondary to Arnold–Chiari malformation or aqueduct stenosis.

# Prevention of neural tube defects

Clear evidence that preconceptual folate supplementation prevents production of neural tube defects.

# Treatment of neural tube defects

- Surgical repair of encephalocele, meningocele, myelomeningocele
- Close observation for development of hydrocephalus and surgical treatment
- Management of bladder and bowels. Possible intermittent bladder drainage
- Orthopaedic management of limb deformities
- Assessment of cognitive abilities
- Treatment of seizures

## 1.3 Hydrocephalus

- Defined as excess fluid within the cranium
- Usually refers to increased volume of cerebrospinal fluid (CSF)

# Production of CSF

- Secreted by choroid plexus (plasma ultrafiltrate, then modified)
- Flows through lateral ventricles, through third and fourth ventricles into posterior fossa and basal cisterns
- Reabsorbed through arachnoid granulations

Terms such ‘communicating’ and ‘non-communicating’ or ‘obstructive’ hydrocephalus are now obsolete.

---

# Main aetiological mechanisms of hydrocephalus

---

Over-secretion	Choroid plexus papilloma
Obstruction:	
Intraventricular	Tumours, malformations, inflammation (post-haemorrhagic)
Extraventricular	Inflammation, tumours, mucopolysaccharidoses
Impaired resorption	Venous sinus compression

---

## Diagnosis (clinical)

- May be asymptomatic
- Irritability
- Headache
- Vomiting
- Drowsiness
- Increased head circumference
- Tense anterior fontanelle
- Splayed sutures
- Scalp vein distension
- Loss of upward gaze (sunsetting)
- Neck rigidity
- Decreased conscious level
- Cranial nerve palsies

## Investigations

- Ultrasonography (when fontanelle open)
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Measurement of CSF pressure by neurosurgical intervention may be indicated

## Management

- Decide need for operation by considering symptoms and rate of head growth
- Surgical:
  - Ventriculostomy
  - Shunting (ventriculoperitoneal, ventriculoatrial)

## 1.4 Disorders of cortical development:

### Lissencephaly

Brain has very few or no gyri, leaving the surface of the brain smooth. Leads to severe motor and learning disability. Some 65% are associated with mutations in the *LIS1* gene. Lissencephaly may be associated with facial abnormalities and a deletion on chromosome 17p 13.3 in Miller–Dieker syndrome.

## **Polymicrogyria**

Increased numbers of small gyri, especially in temporoparietal regions. May be focal or generalized.

## **Periventricular heterotopia**

Aggregation of neurons arrested in their primitive positions. May be part of complex brain malformation syndromes.

## **Pachygyria**

Thickened abnormal cortex. Depending on extent, may lead to cerebral palsy picture or epilepsy.

## **Agenesis of corpus callosum**

Corpus callosum develops between weeks 10 and 12 of embryonic life. Agenesis may be isolated (non-syndromic) or part of a syndrome such as Aicardi syndrome. Extent of other malformations determines disability.

# **1.5 Other nervous system maldevelopments**

## **Dandy–Walker malformation**

Classic Dandy–Walker malformation includes:

- Complete or partial agenesis of cerebellar vermis
- Large cystic formation in posterior fossa due to dilatation of fourth ventricle
- Hydrocephalus, which may not develop until adulthood

May be associated with other cerebral malformations. Considered part of a continuum including the Dandy–Walker variant (part of vermis present, posterior fossa not enlarged) and megacisterna magna (complete vermis, large retrocerebellar cyst).

## **Joubert syndrome**

Familial agenesis of cerebellar vermis, associated with episodic hyperpnoea, ataxia and cognitive impairment

# Aqueduct stenosis

Cause of hydrocephalus in 11% of cases. Aqueduct may be reduced in size or may be represented by numerous channels within aqueduct location. Can occur in X-linked syndrome.

## 2. NEONATAL NEUROLOGY

### 2.1 Neonatal seizures

Seizures are a major neurological problem in the first 28 days of life.

Classification	
Tonic seizures	Stiffening of trunk and extremities
Multifocal clonic seizures	Rhythmic clonic movements of different parts of the body and various seizures
Focal clonic seizures	Repetitive clonic movements of the same part of the body
Subtle seizures	Episodes of stereotyped bicycling, sucking and swallowing movements
Myoclonic seizures	Isolated repetitive brief jerks of the body

### Causes

- Hypoxic–ischaemic encephalopathy
- Intracranial haemorrhage
- Intracranial infection
- Cerebral malformations
- Metabolic disturbances
- Withdrawal seizures
- Familial neonatal convulsions

### 2.2 Hypoxic–ischaemic encephalopathy

The neonatal brain is highly resistant to hypoxia–ischaemia compared with that of an adult. The degree of hypoxia–ischaemia necessary to damage the neonatal brain usually leads to impairment of other organs.

Hypoxia–ischaemia leads to depletion of brain phosphocreatine and ATP. Lactate increases.

### Clinical features

A 5-minute Apgar score of <6, a metabolic acidosis and hypotension are all suggestive of asphyxia in

term infants.

## **Hypoxic–ischaemic encephalopathy in term infants**

Stage 1	Hyperalert, tremulousness, poor feeding. Seizures infrequent
Stage 2	Lethargic, obtunded, hypotonic. Seizures may occur
Stage 3	Comatose. Seizures within 12–24 hours

## **Outcome according to severity of hypoxic–ischaemic encephalopathy**

Stage 1	Largely normal
Stage 2	5% die, 25% suffer neurological injury
Stage 3	80% die, 20% suffer neurological injury

## **2.3 Periventricular–intraventricular haemorrhage**

Usually a disease of preterm infants. Most haemorrhages originate in the subependymal germinal matrix.

### **Potential consequences**

- Asymptomatic
- Catastrophic collapse
- Cerebral infarction
- Post-haemorrhagic hydrocephalus

## **2.4 Periventricular leukomalacia**

This is a pathological term to describe bilateral necrosis of periventricular white matter. Gliosis ensues. It leads to interruption of the fibres responsible for lower limb and optic function, so that periventricular leukomalacia is often the underlying pathology to the spastic diplegia and visual impairment seen in survivors of preterm birth. Evidence now links susceptibility of pre-oligodendrocytes present between 26 and 34 weeks' gestation with production of periventricular leukomalacia.

## **2.5 Brachial plexus injuries**

Traction injury to the brachial plexus can follow difficulty in delivery of the shoulders and head during birth. A large baby, narrow birth canal and malpresentation may all contribute. Usually the

nerve roots are stretched but not completely avulsed. Clavicular or humeral fractures may also occur.

## **Erb palsy**

- C5–6 lesion
- Affects deltoid, serratus anterior, supraspinatus, infraspinatus, biceps, brachioradialis
- Arm is flaccid, adducted and internally rotated
- Elbow is extended, wrist flexed (‘waiter’s tip’)

## **Klumpke paralysis**

- C8–T1 lesion
- Affects intrinsic hand muscles so that flexion of wrist and fingers are affected
- Cervical sympathetic involvement may lead to an ipsilateral Horner syndrome

## **Management**

- Physiotherapy
- Consideration of nerve root surgery

## **3. DISORDERS OF MOVEMENT**

### **3.1 Cerebral palsy**

Cerebral palsy may be defined as a disorder of tone, posture or movement, which is due to a static lesion affecting the developing nervous system. Despite the unchanging nature of the causative lesion, its existence in a developing nervous system means that its manifestations may change over time.

<b>Causes of cerebral palsy:</b>
<p>Prenatal insults:</p> <ul style="list-style-type: none"><li>• Intrauterine hypoxic–ischaemic injury</li><li>• Intrauterine infection</li><li>• Toxins</li><li>• Chromosomal disorders</li></ul>
<p>Perinatal insults:</p> <ul style="list-style-type: none"><li>• Hypoxic–ischaemic injury</li><li>• Intracranial haemorrhage</li><li>• Bilirubin encephalopathy</li></ul>
<p>Postnatal insults:</p>

- Trauma
- Bacterial meningitis
- Viral encephalitis

Epidemiological studies suggest that at least 80% of cases of cerebral palsy are the result of prenatally acquired causes. A minority are the result of intrapartum asphyxia.

## Classification

Based on distribution of motor impairment and tone variations:

- **Spastic** (characterized by fixed increase in muscular tone):
  - Hemiplegia
  - Diplegia
  - Quadriplegia
- **Athetoid** (dyskinetic, dystonic):
  - Athetoid: writhing, involuntary pronation and flexion of distal extremity
  - Choreiform: ‘dancing’ – involuntary rapid semi-purposeful movements of proximal segments of body
- **Ataxic**:
  - Mixed

Spastic diplegia is most frequently seen as the result of periventricular leukomalacia in preterm infants.

Athetoid cerebral palsy may result from either bilirubin encephalopathy or brief profound anoxic–ischaemic episodes.

## Associated clinical features

- Developmental delay
- Tendency to joint contractures
- Epilepsy
- Perceptual difficulties
- Visual and hearing impairment
- Poor growth
- Feeding difficulties

Children with cerebral palsy need the care of a multidisciplinary team.

## 3.2 Ataxia

Acute cerebellar ataxia may occur after a viral infection. Appears to be due to both infectious and post-infectious processes; most commonly follows varicella, plus measles, mumps, herpes simplex, Epstein–Barr virus, Cocksackievirus and echovirus.

Occult neuroblastoma may also lead to acute ataxia.

A common cause is overdosage of drugs such as carbamazepine, phenytoin and benzodiazepines, plus piperazine and antihistamines.

## **Other causes**

- Posterior fossa tumour
- Migraine

## **Ataxia–telangiectasia**

See [Section 13.3](#).

## **Friedreich ataxia**

- Classified as a spinocerebellar degeneration
- Autosomal recessive condition (9cen-q21)
- Gene product frataxin
- Involved in modulation of mitochondrial function

### **Clinical**

- Onset symptoms first or second decade
- Loss of proprioception
- Increasing impairment of cerebellar function
- Development of pes cavus, nystagmus
- Cardiomyopathy develops
- Deterioration so that patients are usually not ambulant in 20s or 30s

### **Treatment**

- Currently symptomatic
- Physiotherapy
- Suitable aids and appliances
- Antioxidant treatment such as idebenone has been shown to be of benefit in delaying cardiac deterioration

## **3.3 Dystonia**



Dystonia is a condition in which muscle tone is abnormal without pyramidal involvement. In many dystonias, muscular tone varies with position of limbs. There may be a dystonic component to cerebral palsy of hypoxic–ischaemic origin, but there are a number of clearly defined syndromes in which dystonia is the main feature.

## **Torsion dystonia (dystonia musculorum deformans)**

- Genetically determined
- Autosomal dominant with incomplete penetrance
- Gene maps to 9q34 in Jewish families (*DYT1*)
- Other unidentified gene responsible in some non-Jewish families

### **Clinical**

- Onset usually after 5 years
- May be focal or generalized
- Dystonia may be task specific, e.g. affected children may not be able to walk forward but can walk backward normally
- Often gradual spread to other parts of the body
- Wilson disease should always be excluded

### **Treatment**

- High-dose anticholinergic drugs
- Occasionally L-dopa

## **Dopa-responsive dystonia**

- Described by Segawa
- Idiopathic dystonia
- Symptoms vary throughout the day
- Onset may be in the first 5 years
- Gene map to 14q22.1-q22.2 (GTP cyclohydrolase 1)
- Symptoms respond dramatically to low-dose L-dopa, which should be continued for life

## **Other important causes of dystonia**

- Wilson disease
- Juvenile Huntington disease

## **3.4 Tics, Gilles de la Tourette syndrome**

Tics are involuntary movements affecting specific groups of muscles so that the affected individual appears to have brief purposeless movements or actions. Tics may be motor or vocal.

## **Simple tics**

- Commonly affect children for a few months in mid-childhood
- Up to 25% of children
- Spontaneous resolution

## **Multiple tics**

- Some children are prone to tics of different type
- Different motor tics, vocal tics
- May not remit entirely

## **Gilles de la Tourette syndrome**

Defined by:

- Multiple motor tics
- One or more vocal tics
- Onset before 21 years of age
- Duration of >1 year

There is probably a continuum between multiple tics and Gilles de la Tourette syndrome.

## **Other characteristic features of Tourette syndrome**

- Echolalia (compulsive repetition of words or phrases just heard)
- Coprolalia (compulsive swearing)
- Attention-deficit disorder and obsessive-compulsive features are present in 50%

## **Treatment**

- Tics may respond to haloperidol, clonidine

# **4. DEVELOPMENTAL DISABILITIES**

## **4.1 Learning disability**

The term 'learning disability' is now generally used in preference to the term 'mental retardation' or 'mental handicap'. It covers a wide variety of conditions in which cognitive functioning is depressed below average levels. In the USA, the term 'mental retardation' is retained, with learning disability

being used to refer to failure to achieve cognitive potential.

Learning disability tends to be grouped according to severity: moderate learning disability usually refers to IQ 50–70, with severe learning disability being defined as IQ <50. The term ‘profound learning disability’ is sometimes used to refer to IQ <20.

The prevalence of learning disability is difficult to estimate. Prevalence of severe learning disability has been estimated at 3–4 per 1000 but, although moderate learning disability is clearly more common, its exact prevalence remains obscure.

## **Aetiology**

This is easier to determine in severe learning disability.

In **severe learning disability**, the following potential causes are recognized:

- Chromosomal
- Genetic
- Congenital anomalies
- Intrauterine insults
- Central nervous system infection
- Familial
- Unknown (about 20%)

## **Moderate learning disability**

- Same range of problems as severe learning disability
- Unknown (55%)

## **Associated problems with learning disability**

- Cerebral palsy
- Visual impairment
- Hearing impairment
- Behavioural difficulties

## **Baseline medical investigations for all children**

- Full history and examination
- Karyotype including fragile X
- Thyroid function tests
- Plasma amino acids
- Urine mucopolysaccharide screen
- Plasma creatine kinase (in boys aged <5 years)

Other tests may be indicated, depending on clinical features.

## 4.2 Autism

Autism is a disorder characterized by:

- Disturbance of reciprocal social interaction.
- Disturbance of communication (including language, comprehension and expression)
- Disturbance of behaviour, leading to restriction of behavioural range

All the above findings may be seen in learning-disabled individuals.

### **Associated features in autism**

- Learning disability
- Epilepsy
- Visual impairment
- Hearing impairment

### **Asperger syndrome**

Often considered to be on the autistic spectrum. Characterized by autistic features in individuals of otherwise normal intelligence. Specifically characterized by:

- Impairment in social interaction.
- Stereotypical behaviour
- No specific impairment of language

## 4.3 Attention-deficit hyperactivity disorder (ADHD)

Some children show impulsive, hyperactive behaviour together with poor concentration and attention. These children are usually of normal intelligence, although functionally they may achieve less than their peers. Medication such as methylphenidate or dexamfetamine may be effective.

## 4.4 Deficits in attention, motor control and perception (DAMP)

- Often described as ‘minimal brain damage’ in older literature
- Deficit in motor control and perception often referred to as ‘dyspraxia’
- Another term for motor difficulties is ‘developmental coordination disorder’ (DCD)
- Children have difficulties as described in varying degrees
- Treatment needs to include assessment, but also educational help and a physical programme

(occupational therapy)

## 5. EPILEPSY

### 5.1 Diagnosis

Diagnosis of ‘fits, faints and funny turns’ is based primarily on clinical assessment of such events with recognition of characteristic patterns, supported by the results of special investigations.

### 5.2 Definition and classification

Epileptic seizures are clinical events that result from abnormal, excessive electrical discharge from cerebral neurons.

Epilepsy is the tendency to have recurrent, usually unprovoked, epileptic seizures.

The classification of epilepsies can be approached from the viewpoint of the characteristics of individual seizures or by identification of epileptic syndromes.

International Classification of Epileptic Seizures (modified from International League against Epilepsy Classification)		
Partial seizures	Simple partial seizures (no disturbance of consciousness)	With motor signs
		With somatosensory symptoms
		With autonomic symptoms
		With psychic symptoms
Generalized seizures	Complex partial seizures (disturbance of consciousness)	
	Partial seizures with secondary generalization	
	Absence seizures (typical)	
	Absence seizures (atypical):	
	Myoclonic seizures	
	Clonic seizures	
	Tonic seizures	
	Tonic–clonic seizures	
	Atonic seizures	

Localization related epilepsies	Idiopathic	Benign childhood epilepsy with centrotemporal spikes (‘benign rolandic epilepsy’)
		Childhood epilepsy with occipital paroxysms
	Symptomatic	Temporal lobe epilepsy
		Frontal lobe epilepsy
		Parietal lobe epilepsy
		Occipital lobe epilepsy
		Epilepsia partialis continua
Generalized epileptic syndromes	Idiopathic	Benign neonatal familial convulsions
		Benign neonatal convulsions
		Benign myoclonic epilepsy of infancy
		Childhood absence epilepsy
		Juvenile absence epilepsy
		Juvenile myoclonic epilepsy
		Epilepsy with grand mal seizures on waking
	Symptomatic/ cryptogenic	West syndrome (infantile spasms)
		Lennox–Gastaut syndrome
		Myoclonic–astatic epilepsy
	Symptomatic	Early myoclonic encephalopathy
		Ohtahara syndrome
Epileptic syndromes unclassified as focal or generalized		Neonatal seizures
		Severe myoclonic epilepsy in infancy
		Epilepsy with continuous spike-waves in slow-wave sleep
		Landau–Kleffner syndrome

5.3 Generalized epilepsies

Absence seizures

Typical absence seizures, previously termed ‘petit mal epilepsy’, is characterized by brief (5–20 s) episodes of staring during which the child is unaware of his or her surroundings. Associated with 3-

Hz spike and wave discharge on EEG. Can be precipitated by hyperventilation. Drugs of choice: sodium valproate, ethosuximide, lamotrigine.

Atypical absences: EEG shows pattern of different frequency.

## Myoclonic seizures

Brief sudden generalized muscular jerks. Drugs of choice: sodium valproate, benzodiazepines, lamotrigine. May be exacerbated by carbamazepine.

## Infantile spasms

Onset in first 12 months – brief sudden muscular contractions resulting in extension or flexion of the body. Attacks occur in runs. Associated with disorganized EEG described as hypsarrhythmia, as well as developmental arrest or regression. May be idiopathic or symptomatic (causes include tuberous sclerosis, perinatal hypoxic–ischaemic injury, inborn errors of metabolism). Treatment of choice: corticosteroids (or adrenocorticotrophic hormone or ACTH) or vigabatrin

## Juvenile myoclonic epilepsy

Onset in adolescence – myoclonic seizures on wakening from sleep. Treatment of choice: sodium valproate; carbamazepine may exacerbate seizures.

## 5.4 Partial epilepsies

<b>Benign childhood epilepsy with centrotemporal spikes</b> ('benign rolandic epilepsy')	Characterized by predominantly nocturnal partial seizures with a slight male preponderance. Seizures may affect face or upper limbs; speech arrest may occur. Excellent prognosis for remission
<b>Complex partial seizures</b>	Characterized by stereotypical behaviour, loss of consciousness and focal EEG abnormalities. Often arise from temporal lobe foci. May respond to carbamazepine or sodium valproate

## 5.5 Assessment and treatment of epilepsy

- Clinical assessment of seizure type and frequency
- EEG allows more specific classification of seizure type; if standard EEG is normal and further EEG confirmation is necessary in the face of clear clinical history of epileptic seizures, then sleep or sleep-deprived EEG may document abnormalities
- Imaging (MRI) is indicated in partial seizures and generalized seizures resistant to treatment

# Management

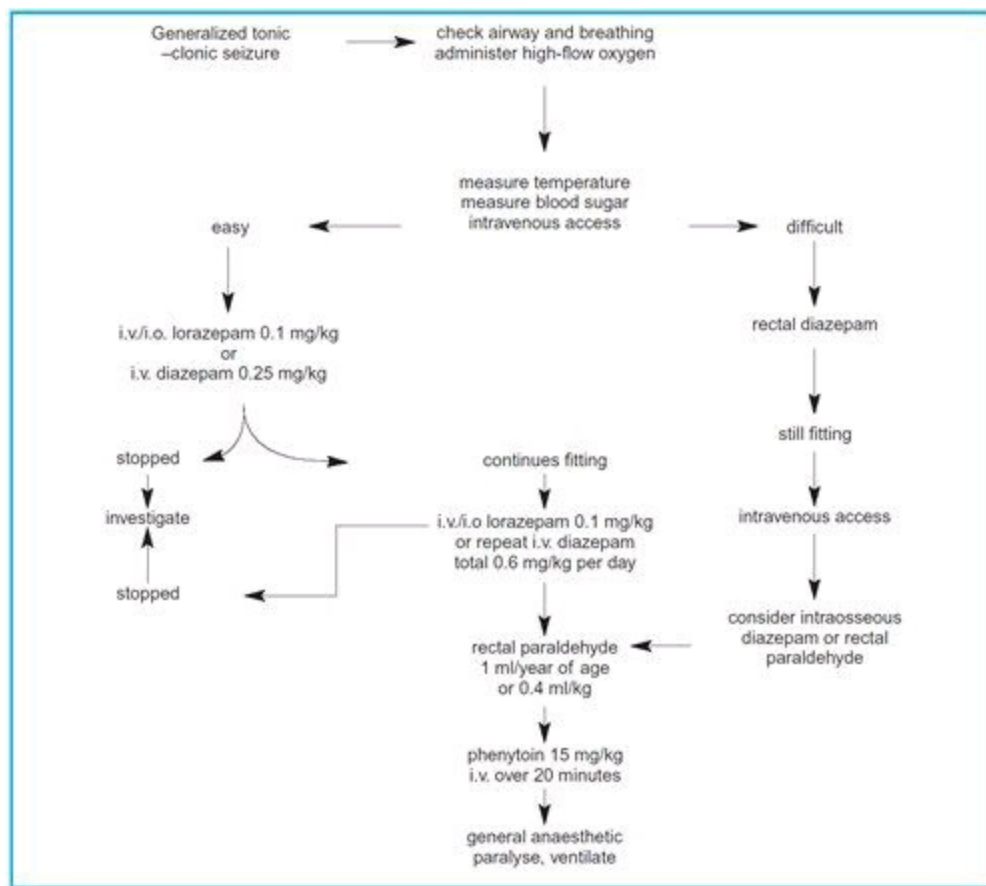
- Explanation of potential risks and benefits of different therapies
- Medication – start, depending on frequency and number of seizures
- Maintenance of seizure freedom with medication for perhaps 2 years
- Subsequent withdrawal of medication
- Some forms of partial epilepsy may be amenable to epilepsy surgery; when seizure disorder is intractable, site of seizure onset can be localized, site is non-eloquent brain
- Other forms of treatment – steroids, ketogenic diet, vagal nerve stimulation

## 5.6 Anticonvulsant drugs

Drug	Used for seizure types	Dose range	Side effects	Notes
Carbamazepine	Partial seizures Generalized tonic-clonic seizures	15–25 mg/kg per day	Ataxia, sedation, leukopenia, thrombocytopenia, rash	
Sodium valproate	All seizure types	20–40 mg/kg per day	Nausea, vomiting, abdominal pain, tremor, hair loss, thrombocytopenia, liver function abnormalities	
Lamotrigine	All seizure types	With valproate: 5 mg/kg per day Without valproate: 15 mg/kg per day	Rash	Not licensed as monotherapy for under 12 years
Vigabatrin	Partial seizures West syndrome	50–150 mg/kg per day	Sedation, visual field constriction	
Ethosuximide	Absences	20–50 mg/kg per day	Gastrointestinal disturbance, rash	
Gabapentin	Partial seizures	Up to 45 mg/kg per day	Sedation	
Oxcarbazepine	Partial/generalized seizures	30 mg/kg per day	Sedation, rash	
Topiramate	All seizure types	6–9 mg/kg per day	Sedation, anorexia, paraesthesiae	
Clobazam	All seizure types	2 mg/kg per day	Sedation	
Clonazepam	All seizure types	2 mg/kg per day	Sedation	
Phenytoin	All seizure types	5 mg/kg per day	Nausea, vomiting, diarrhoea, rash, peripheral neuropathy	Measure level
Phenobarbital	All seizure types	5–8 mg/kg per day	Sedation	Measure level
Levetiracetam	Partial seizures	50–60 mg/kg per day	Sedation	Not licensed as monotherapy for under 16 years
Tiagabine	Partial seizures	30–45 mg/kg per day	Sedation	Not licensed for under 12 years

## 5.7 Management of status epilepticus





## Prognosis

Of children with epilepsy 70% are seizure-free by their sixteenth birthday. Remission is less likely in: partial epilepsy, symptomatic epilepsy, some epilepsy syndromes such as juvenile myoclonic epilepsy or epileptic encephalopathies such as Lennox–Gastaut syndrome.

## 6. NON-EPILEPTIC SEIZURES

### 6.1 Anoxic seizures

Anoxic (or anoxic–ischaemic) seizures form a group of paroxysmal disorders that are often the main differential diagnosis to epilepsy. Diagnosis is predominantly by clinical assessment. There are two important types seen in childhood: breath-holding attacks and reflex anoxic seizures.

**Breath-holding attacks** are seen in young children, often in the setting of a tantrum. The thwarted child screams and holds his or her breath, becoming cyanosed and sometimes exhibiting subsequent convulsive movements. It may be possible to encourage the child to take a breath by gently blowing on his face. The tendency to have such episodes abates as children become older.

**Reflex anoxic seizures** are the clinical manifestation of vagocardiac attacks. The precipitant may be a sudden, unexpected, painful stimulus or occasionally vomiting. Increased sensitivity of the vagus nerve leads to bradycardia, or even brief asystole, in turn leading to pallor and cerebral anoxia–ischaemia. After collapse, the child may then exhibit convulsive movements. Recovery is

spontaneous. Apart from the risk of injury during a collapse, the prognosis is good with few, if any, individuals having adverse cerebral effects. The tendency to have such attacks improves with age but is often not completely abolished. Diagnosis can be confirmed by eliciting bradycardia under controlled monitoring conditions through the exertion of eyeball pressure.

## 6.2 Psychogenic seizures

A small proportion of children have episodes of collapse, or even epileptiform attacks, that are under conscious or subconscious control. The trigger for these episodes is usually some form of psychological disturbance, which may be deeply hidden.

The nature and setting of the attack are often a clue to the event. The attack itself may include sudden collapse without, for example, pallor or an epileptiform attack during which the child may respond to his or her surroundings. The setting of the attack is often to gain maximum attention for the episode. There is often some form of behavioural trigger to elicit an event.

Prolonged EEG and ECG monitoring may be helpful in supporting the diagnosis and helping families accept the nature of the attack.

Management is via psychological or psychiatric treatment.

## 7. HEADACHES

Headache is a common complaint in childhood. Population studies estimate that up to 35% of children have complained of headache at some time. The most common cause of headache in western populations is tension or psychogenic headache.

Classification of headache
Tension or psychogenic headache
Migraine
Vascular disorders <ul style="list-style-type: none"><li>• Subarachnoid haemorrhage</li><li>• Hypertension</li><li>• Arteriovenous malformation</li></ul>
Headaches related to raised intracranial pressure <ul style="list-style-type: none"><li>• Tumours</li><li>• Hydrocephalus</li><li>• Benign intracranial hypertension</li><li>• Subdural haematoma</li></ul>

## Inflammatory disorders

- Meningitis
- Vasculitis

## Referred pain

- Sinusitis
- Optic neuritis
- Otitis media

## Miscellaneous

- Refractive errors
- Carbon monoxide poisoning
- Substance abuse

# 7.1 Tension headaches

- Often occur daily
- Generalized, dull – may involve band-like compression around head
- Worsens over the day
- Worse with stress
- Normal examination
- Anxious or depressed affect
- Depressive features in history

## Management

- Reassurance
- Supportive psychotherapy

# 7.2 Migraine

Defined as ‘a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with neurological and mood disturbance. All of the above characteristics are not necessarily present in each attack or in each patient’.

## Classification of migraine:

- Common migraine (no aura)
- Classic migraine (aura preceding onset of headache)
- Complicated migraine (persisting neurological deficit after migraine attack)

- Basilar migraine
- Migraine variance
- Cluster headaches

## Treatment

- **Acute:** analgesics, relaxation, occasionally antiemetics
- **Prophylaxis:** avoidance of triggers such as cheese, medication such as pizotifen, propranolol

## 7.3 Other headaches

### Post-traumatic headache

Following concussive head injury. May last several months, then resolves. May persist in the setting of depression or ongoing litigation.

### Headache due to raised intracranial pressure

Worse in early morning. Worse with coughing and bending.

## 8. ABNORMALITIES OF HEAD SIZE AND SHAPE

Brain growth is usually the most important determinant of head growth. In full-term infants, the rate of head growth in the first 3 months is 2 cm/month, in the second 3 months 1 cm/month and in the subsequent 6 months 0.5 cm/month.

### 8.1 Macrocephaly

Consider:

- Familial microcephaly
- Hydrocephalus
- Chronic subdural haematomas
- Associated disorders such as tuberous sclerosis or neurofibromatosis
- Metabolic conditions

Investigations depend on rate of growth, deviation from normal and presence of absence of abnormal neurological signs.

## Treatment

If necessary, this is based on underlying pathology.

## 8.2 Microcephaly

Defined as occipitofrontal head circumference, below two standard deviations for age, sex and gestational age.

Consider:

- Insults during pregnancy
- Perinatal insults
- Encephalopathies in infancy
- Autosomal recessive microcephaly

## Investigations

- Chromosomes
- Antibodies to congenital infections
- Metabolic screen
- MRI
- Consider measurement of maternal plasma amino acids to exclude maternal phenylketonuria

## 8.3 Abnormal head shape

May be associated with specific syndrome, e.g. achondroplasia or Down syndrome. May be the result of craniosynostosis.

## Craniosynostosis

Premature closure of one or more cranial sutures. Ultimate skull deformity will depend upon which sutures are involved and the timing of their fusion.

Head shape	Description	Sutures involved	Problems
Scaphocephaly Brachycephaly	Elongated narrow skull Short, broad skull	Sagittal Both coronal	Cosmetic Associated anomalies such as learning disability
Plagiocephaly	Unilateral flattening of skull	Single coronal (occasionally lambdoid)	Cosmetic
Trigonocephaly	Narrow, pointed forehead	Metopic	Possible associated forebrain abnormalities
Oxycephaly (acrocephaly)	High pointed head	Coronal, sagittal, lambdoid	Apert and Crouzon syndromes (see below)

## Apert syndrome

Acrocephaly, facial underdevelopment, syndactyly, learning disability.

## **Crouzon syndrome**

Acrocephaly, scaphocephaly or brachycephaly, hypertelorism, exophthalmos, increased intracranial pressure, learning disability.

## **9. NEUROMUSCULAR DISORDERS**

### **9.1 The floppy infant**

It is important to realize that much of the process leading to a diagnosis in the floppy infant is the clinical assessment of the infant by history and examination. It is this assessment that should direct diagnostic investigations. In an era when specific genetic tests for conditions are increasingly available, a clearer idea of possible diagnoses is even more important.

#### **Causes of hypotonia in infants**

##### **General health**

- Prematurity
- Intercurrent illness
- Ligamentous laxity

##### **General: neurological**

- Chromosomal abnormalities e.g Down syndrome
- Prader–Willi syndrome
- Hypoxic–ischaemic brain injury (especially early basal ganglia injury)
- Metabolic conditions
  - aminoacidurias
  - organic acidurias
  - peroxisomal disorders

##### **Spinal**

- Cervical cord injury

##### **Anterior horn cell**

- Poliomyelitis
- Spinal muscular atrophy

## **Peripheral nerve**

- Peripheral neuropathies

## **Neuromuscular junction**

- Transient myasthenia
- Congenital myasthenic syndrome

## **Muscle**

- Congenital muscular dystrophy
- Congenital myopathies
- Congenital myotonic dystrophy

## **9.2 Duchenne muscular dystrophy**

Duchenne muscular dystrophy is easily the most common neuromuscular condition seen in western European practice.

- Inherited as X-linked recessive condition
- One-third are new mutations
- Incidence 1 in 3500 male births
- Female carriers usually asymptomatic, occasionally manifesting carriers

## **Molecular genetics**

- Due to mutations in dystrophin gene
- Gene approximately 2 million base pairs
- Duchenne muscular dystrophy patients produce no dystrophin
- Becker muscular dystrophy (allelic, milder form) patients produce abnormal but functional protein
- Dystrophin localized to muscle cell membranes

## **Clinical features**

- Onset in early years
- Some cases identified presymptomatically by abnormal transaminases measured during intercurrent illness
- Sometimes leads to failure to thrive
- Early delay in motor milestones
- Difficulties in climbing stairs
- Lordosis with waddling gait

- Pseudohypertrophy of calves
- Progressive muscular weakness
- Tendency to joint contractures
- Typically, boys lose ability to walk between 8 and 12 years
- When dependent on wheelchair, boys are prone to develop scoliosis
- Respiratory failure supervenes

Also:

- Increased incidence of learning disability
- Cardiomyopathy occurs
- Survival to late teens, early twenties

## Diagnosis

- High plasma creatine kinase ( $>5000$  IU/l)
- Mutations in dystrophin gene
- Muscle biopsy – dystrophic picture with absent dystrophin

## Treatment

- No curative treatment
- Physiotherapy
- Corticosteroids
- Appropriate seating
- Respiratory support e.g. non-invasive ventilation
- Aggressive treatment of cardiac failure
- Management of scoliosis

## 9.3 Becker muscular dystrophy

- Allelic disease to Duchenne muscular dystrophy
- Milder than Duchenne muscular dystrophy
- Patients walk beyond 16 years of age
- Similar clinical pattern to Duchenne muscular dystrophy
- Cramps can be problematical
- Prone to cardiomyopathy

## Diagnosis

Duchenne muscular dystrophy and Becker muscular dystrophy distinguished clinically and on muscle biopsy findings. Nature of genetic mutation can give pointer as to severity of condition but current routine genetic testing does not distinguish reliably between Duchenne and Becker muscular



dystrophy; it just identifies a dystrophinopathy.

## 9.4 Other muscular dystrophies and congenital myopathies

Muscular dystrophies are characterized by dystrophic muscle histopathology: muscle fibre necrosis and regeneration with increased fat and connective tissue. May be progressive or static.

### **Emery–Dreifuss muscular dystrophy**

- Uncommon X-linked muscular dystrophy (Xq28)
- Mild proximal muscular weakness
- Joint contractures
- Cardiac involvement – affected individuals may be prone to sudden cardiac death

### **Facioscapulohumeral muscular dystrophy**

- Autosomal dominant muscular dystrophy (4q35)
- Facial, scapular and humeral wasting and weakness
- Slowly progressive
- Other muscles may be involved
- Variable expression within families

### **Limb–girdle muscular dystrophies**

- Common on a worldwide basis
- May be inherited as autosomal dominant (AD) or autosomal recessive (AR) traits (at least three separate AD and nine AR limb–girdle muscular dystrophies identified so far)
- Variations in clinical phenotype
- Many are similar to Duchenne muscular dystrophy or Becker muscular dystrophy

### **Congenital muscular dystrophies**

This is a group of disorders in infants characterized by muscular weakness, hypotonia and joint contractures from birth.

- Muscle biopsy shows typical dystrophic changes
- Different subtypes now being described

### **Merosin-negative congenital muscular dystrophy**

- Characterized by absence of merosin on muscle biopsy
- Clinically hypotonia, weakness, contractures
- Often associated with learning disability

- Functionally, affected children do not achieve independent walking

## **Merosin-positive congenital muscular dystrophy**

- Clinically less severe than merosin-negative congenital muscular dystrophy

## **Congenital muscular dystrophies associated with abnormal glycosylation of $\alpha$ -dystroglycan**

- AR
- As well as severe weakness, affected individuals have brain malformations
- Clinical syndromes include Fukuyama congenital muscular dystrophy (CMD), muscle–eye–brain disease and Walker–Warburg syndrome
- Genes include *FCMD*, *POMGnT1*, *FKRP*, *LARGE*, *POMT1*

## **Congenital myopathies**

A group of disorders characterized by hypotonia and weakness from birth. Differentiated on clinical and histological features:

- Central cord disease
- Nemaline myopathy
- Myotubular myopathy
- Congenital fibre type disproportion

## **Myotonic dystrophy**

- Common (incidence 13.5 per 100 000 live births) neuromuscular condition
- AD inheritance (*DM1*: 19q13) (*DM2* predominantly in adults)
- Severity appears to be related to size of triplet repeat (CTG) in gene mutation

## **Congenital myotonic dystrophy**

- Condition often unrecognized in mothers
- Preceding polyhydramnios
- Baby often born unexpectedly ‘flat’
- Facial weakness, hypotonia
- Often requires respiratory support
- Joint contractures, especially talipes

## **Myotonic dystrophy in older children and adults**

- Facial weakness initially
- Then weakness affecting temporalis, sternomastoid, distal leg muscles

- Progressive weakness
- Difficulties in relaxing muscular contraction, e.g. difficulties in relaxing grip
- Cardiac involvement

## Diagnosis

- Gene mutation analysis
- Electromyogram in older children upwards (>3–4 years of age) shows characteristic ‘dive bomber’ discharges

## Myotonia congenita (Thomsen disease)

- Rare
- Autosomal dominant inheritance
- Characterized by myotonia, cramps
- Muscular hypertrophy is typical

## 9.5 Anterior horn cell disease

### Spinal muscular atrophy

The spinal muscular atrophies are a group of heterogeneous conditions that are characterized by the clinical effects of anterior horn cell degeneration. The most common spinal muscular dystrophies (SMAs) in childhood are the autosomal recessive proximal SMAs.

#### Clinical

- Symmetrical muscle weakness of trunk and limbs, more marked proximally than distally and in legs more than arms
- Tongue fasciculation
- Investigations confirming neurogenic abnormalities

#### Genetics

- AR
- Gene at chromosome 5q11-13
- Disease caused by mutations of *SMN* gene
- Severity determining mechanism remains unclear

Childhood onset proximal spinal muscular atrophies				
Severity		Synonyms		Functional abilities

Severe	Type I, acute, Werdnig–Hoffmann disease	Unable to sit or walk
Intermediate	Type II	Able to sit but not walk
Mild	Type III, Kugelberg–Wielander disease	Able to walk

## Severe SMA

- Incidence 1 in 20 000 live births
- In approximately 30% onset is prenatal
- Symmetrical weakness
- Paralysis of intercostal muscles
- Absent deep tendon reflexes
- Tongue fasciculation
- Death occurs within first 18 months from respiratory failure/infection

## Diagnosis

- Electromyography (EMG)
- Muscle biopsy
- Genetic analysis

## Intermediate SMA

- Autosomal recessive
- Usual onset after 3 months
- Infant learns to sit
- Prone to early scoliosis
- Prognosis depends on degree of respiratory muscle involvement

## Mild SMA

- AR
- Able to walk, but proximal weakness evident
- Tendon jerks may not be absent

## 9.6 Neuropathies

Hereditary motor and sensory neuropathies (HMSNs) are the most common degenerative disorders of the peripheral nervous system. Often known by their eponymous title Charcot–Marie–Tooth disease (CMT) or peroneal muscular atrophy.

Previously X-linked, AR and AD forms were recognized, but the advent of molecular genetics has identified numerous genetically distinct forms (see table).

Clinically, affected individuals develop slowly progressive distal weakness with areflexia. In the early phases, foot drop is often the main clinical problem. In later stages, which in the common forms may be several decades after onset, hand weakness, joint deformity and distal sensory loss may be problematical.

## Hereditary motor and sensory neuropathies (Charcot–Marie–Tooth disease [CMT])

Type	Inheritance	Genetic defect	Gene	Neurophysiology	Onset
<b>Type I (demyelinating)</b>					
CMT 1A	AD	Duplication 17p11.2	<i>PMP22</i>	Low motor nerve conduction velocity	First decade
CMT 1B	AD	1q21-q23	<i>P<sub>0</sub></i>		
CMT 1C	AD	16p13	<i>LITAF/SIMPLE</i>		
CMT 4	AR	8q (one type)	<i>GDAP1</i>		
<b>Type II (axonal)</b>					
CMT 2A	AD	1p36	<i>KIF1B</i>	Normal motor nerve conduction velocity	Second to third decades
CMT 2B	AR	3q21	<i>RAB</i> missense		
<b>Type III (hypertrophic)</b>					
Dejerine–Sottas	AD	17p11.2 and others 1q21-q23	<i>PMP22</i> and others <i>P<sub>0</sub></i>	Low motor conduction velocity	First year
<b>X-linked forms</b>					
CMT X	XL	Xq13.1	Connexin 32		

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

HMSN and Friedreich ataxia are sometimes confused. In HMSN, there is areflexia and evidence of distal weakness. In Friedreich ataxia there is much more clear ataxia with evidence of loss of joint position sense. On neurophysiological testing, HMSN patients have abnormal motor conduction, whereas Friedreich ataxia patients have evidence of a sensory neuropathy.

## 9.7 Acute neuromuscular disorders

### Guillain–Barré syndrome

Acute demyelinating disease of peripheral nerves characterized by progressive weakness:

- Usually follows viral infection or immunization
- Numerous other infections including *Campylobacter jejuni* – gastroenteritis has been implicated

#### Clinical features

- Sudden onset of weakness, usually affecting lower limbs
- Ascending paralysis
- Usually symmetrical weakness
- Pain often prominent feature
- Sensory involvement in about 50%

- Respiratory muscle weakness may occur

## **Diagnosis**

- High CSF protein
- A marked slowing of motor neuron conduction velocity
- Conduction block

## **Course**

- Deterioration over the first 10–20 days
- Plateau
- Recovery
- Mortality rate 2–3% in children

## **Treatment**

- Symptomatic
- Respiratory support
- Plasma exchange
- High-dose immunoglobulin

## **Juvenile dermatomyositis**

- Systemic illness affecting primarily skin, muscles and gastrointestinal tract
- Unlike adult dermatomyositis, juvenile dermatomyositis is not associated with malignancy

## **Clinical**

- Age of onset 5–10 years
- May present with fever, muscle pain
- Onset can be insidious
- Increasing muscular weakness, mainly proximal
- Rash involving upper eyelids (heliotrope rash) and periorbital region develops
- Rash on extensor surfaces. Calcinosis is a feature
- May have difficulty swallowing
- Children are often miserable in advance of other symptoms

## **Diagnosis**

- Creatine kinase may or may not be raised
- Muscle biopsy may show perifascicular atrophy, but changes can be patchy

## **Treatment**

- Corticosteroids
- Other immunosuppressive treatment such as methotrexate or ciclosporin

## 9.8 Disorders of neuromuscular junction

### Myasthenia gravis

- Most common disease of the neuromuscular junction
- Caused by antibodies directed against postsynaptic acetylcholine receptors

### Clinical features

- Onset after 1 year
- Adolescent girls most commonly affected
- Generalized form affects extraocular muscles first
- Then goes on to affect proximal limbs and bulbar muscles
- Variable natural course

### Diagnosis

- Edrophonium test
- EMG confirming neuromuscular block
- Demonstration of anti-acetylcholine receptor antibodies

### Treatment

- Anticholinesterase drugs
- Immunosuppressants
- Thymectomy
- Plasma exchange or immunoglobulin infusion acutely

### Other myasthenic syndromes

There are rare congenital myasthenic syndromes that result from specific defects in the process of neuromuscular transmission. Some affect presynaptic mechanisms, others postsynaptic components. Some of these infants may have joint contractures.

## 10. CNS INFECTIONS AND PARAINFECTIONOUS DISORDERS

### 10.1 Meningitis

Acute bacterial meningitis remains an important cause of neurological morbidity in childhood. Causative organisms vary depending on the age of the child and the pattern of infection has been altered by changing immunization patterns.

Age	Organism
Neonatal	Group B streptococci
	<i>Escherichia coli</i>
	<i>Listeria monocytogenes</i>
	<i>Staphylococcus aureus</i>
First two months	Group B streptococci
	<i>Escherichia coli</i>
	<i>Haemophilus influenzae</i>
	<i>Streptococcus pneumoniae</i>
Older infants and young children	<i>Haemophilus influenzae</i>
	<i>Neisseria meningitidis</i>
	<i>Streptococcus pneumoniae</i>

### Clinical features

In neonates, meningitis is usually part of septicaemic illness. Symptoms and signs may be non-specific: lethargy, poor feeding, respiratory distress. Neck stiffness is rarely seen.

In young infants also, signs may be non-specific and meningeal irritation may be absent.

In older children, signs are more typical: lethargy, headache, photophobia, neck stiffness. Meningococcaemia is associated with a haemorrhagic rash.

### Outcome

Neurological sequelae may occur in up to 30% of children: focal neurological deficits, learning disability, hydrocephalus and deafness may all occur. Mortality is improving with earlier diagnosis and treatment.

### Diagnosis

Lumbar puncture and CSF analysis are definitive. The white cell count is raised with a predominance of neutrophils, CSF glucose is reduced and protein is raised. Gram staining of CSF and immunoassays may allow identification of the organism. However, lumbar puncture is contraindicated if signs of raised intracranial pressure are present or if consciousness is impaired. Treatment then needs to be aimed at the most likely organisms. Blood cultures can be taken before starting treatment.

### Management

- Antibiotic treatment – agent will depend on age of patient and likely infecting organism
- Watch for subdural effusions and hydrocephalus – measure head circumference



- Evidence re steroid use to prevent neurological sequelae unclear – some evidence to support prevention of deafness in *H. influenzae* meningitis

Viral meningitis may result from a wide variety of viruses: Coxsackievirus, echoviruses, mumps, measles, herpes simplex, poliomyelitis, varicella-zoster.

- Symptoms similar to bacterial meningitis, but less pronounced
- Specific diagnosis may be suggested by other disease stigmata
- CSF clear with lymphocytosis
- Prognosis of uncomplicated viral meningitis good

## **Tuberculous meningitis**

Generally occurs within 6–8 weeks of primary pulmonary infection or during miliary tuberculosis (TB). Most common in age range 6 months to 3 years.

Leads to basal arteritis, which may cause hydrocephalus and cranial neuropathies. Symptoms otherwise often non-specific – lethargy, fever, headache.

CSF – high white cell count, predominantly lymphocytes, raised protein often >2 g/l, low glucose; tuberculous cultures may be positive.

## **Treatment**

- Anti-tuberculous chemotherapy
- Optimal treatment not determined
- Usually triple therapy (rifampicin, isoniazid, pyrazinamide) for at least 6 months but many authorities suggest a fourth drug for the first 3 months
- The place of corticosteroids is unclear but these are often used in the first few months to reduce inflammation

Mortality and morbidity remain high despite treatment.

## **10.2 Encephalitis**

Numerous viruses may lead to inflammation of the brain: herpes viruses, adenoviruses, arboviruses and enteroviruses, for example. The underlying causative agent in undiagnosed encephalitis may remain obscure. It is therefore usual practice to treat with cefotaxime/ceftriaxone, aciclovir and erythromycin/azithromycin until results are available.

Clinical features – confusion, coma, seizures, motor abnormalities. Infection usually starts to resolve 7–14 days after the onset. However, recovery may be delayed for several months.

# Herpes simplex encephalitis

- Common
- Often focal brain inflammation, located in temporal lobes
- High mortality and morbidity rates (50%)
- Specific treatment: aciclovir

## Investigations for encephalitis

- CSF examination/cultures
- EEG
- Brain imaging
- Occasionally, brain biopsy

## Treatment

- Supportive (fluid management/ventilation if necessary)
- Aciclovir

## 10.3 Immune-mediated and other infectious disorders

### Sydenham chorea

- Main neurological feature of rheumatic fever
- Chorea results from immune reaction triggered by group A streptococcal infection
- May be associated with emotional lability
- Probably overlaps with PANDAS (psychiatric and neurological diseases associated with streptococcal infection)
- In about 75%, chorea resolves within 6 months

### Anti-NMDA receptor encephalitis

Recently recognized, this disorder is caused by antibodies to *N*-methyl-D-aspartate receptor. Usually preceded by intercurrent illness, some cases are associated with mycoplasma infection (see below).

- Movement disorder (chorea, dystonia)
- Autonomic instability
- Neuropsychiatric symptoms
- Seizures

Treatment is with immunomodulation: corticosteroids, immunoglobulin, plasma exchange, cyclophosphamide, rituximab.

# Subacute sclerosing panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a slow viral infection, caused by an atypical response to measles infection. Exposure to measles is usually in the first 2 years. Risk of SSPE is higher after contracting natural measles, compared with that after measles immunization. Median interval between measles and SSPE is 8 years.

- Subtle deficits initially
- Increasing memory difficulties
- Worsening disabilities: seizures, motor difficulties, learning disability

## Mycoplasma encephalitis

*Mycoplasma pneumoniae* is the most common cause of community acquired pneumonia in adults and commonly leads to infection in children. It may cause encephalitis, predominantly through immune-mediated mechanisms that may respond to steroid administration. The evidence base is small.

## Acquired immune deficiency syndrome

This is caused by human immunodeficiency virus (HIV), an RNA retrovirus that eventually leads to the death of its host cell T4+ lymphocyte.

### Neurological features

- Neurological features of opportunistic infection such as meningitis or encephalitis
- Dementia

## 11. CEREBROVASCULAR DISEASE

### 11.1 Arterial occlusion

- May result from embolism or thrombosis

Effects of arterial occlusion	
Internal carotid artery	Hemiplegia, hemianopia, aphasia if dominant hemisphere
Middle cerebral artery	Hemiplegia with upper limb predominance, hemianopia, aphasia if dominant hemisphere
Anterior cerebral artery	Hemiplegia affecting predominantly lower limbs
Posterior cerebral	Homonymous hemianopia, ataxia, hemiparesis, vertigo

artery

## Investigations

MRI

MR angiography

Possible formal angiography

Carotid Doppler studies

Echocardiography

Full blood count, plasma homocysteine

Clotting studies, especially factor V Leiden, prothrombin 20210A, lipoprotein (a)

The place of measurement of antithrombin III protein C and protein S in the genesis of childhood stroke remains debatable.

## 11.2 Venous thrombosis

- Less common than arterial occlusion
- Produces a variable clinical picture:
  - Intracranial hypertension
  - Seizures
  - Focal neurological signs

### Causes

- Sepsis:
  - Otitis media
  - Sinusitis
  - Cutaneous infection
- Dehydration
- Coagulopathy

### Treatment

- Disputed
- Heparin may be given in the acute phase

## 12. NEURO-ONCOLOGY

Brain tumours are the second most common malignancy in children after leukaemia. In infants, supratentorial tumours predominate, whereas, in older children, infratentorial tumours are much more common. The trend reverses in children over 8 years of age with a slight preponderance of

supratentorial tumours.

Central nervous system (CNS) tumours are of varying degrees of malignancy. Those that do metastasize tend to do so within the CNS. It is also important to note that a ‘benign’ tumour situated so that it cannot be removed may have a more serious effect than a ‘malignant’ tumour differently situated.

General symptoms and signs associated with brain tumours in children may include headache, vomiting, papilloedema, cranial nerve palsies and other focal symptoms such as ataxia.

## 12.1 Posterior fossa tumours

### Cerebellar astrocytoma

This is the most common tumour in children; it may involve the vermis or the cerebellar hemispheres or both. Most are cystic and slow growing.

- Treatment is surgical. Occasionally more malignant tumours require radiotherapy also

### Medulloblastoma

Common tumour. Highly malignant, rapidly growing. Arises from the cerebellar vermis. Often leads to hydrocephalus. May metastasize along CSF pathways. Often solid tumours.

- Treatment – surgery and radiotherapy. Trials have sought to clarify the position of chemotherapy
- Outlook has improved: 75% 5-year survival, 50% 10-year survival. Prognosis poorer in young children. Evidence is emerging that specific genetic constitution of tumour is most important in determining outcome

### Ependymoma

Makes up 6–10% of childhood tumours. Arises from fourth ventricle. May lead to hydrocephalus and may metastasize.

- Treatment – surgical resection and radiotherapy
- Poor 5-year survival often related to localization of tumour

	Percentage total tumours in childhood	Spread	Location	Structure	Treatment	Five-year survival rate (%)
Astrocytoma	14–20	Local	Vermis/cerebellar hemispheres	Cystic	Surgery	About 100
Medulloblastoma	14–20	CSF pathways	Vermis	Usually solid	Surgery/radiotherapy/ chemotherapy	75–80
Ependymoma	6–10	CSF pathways	Floor fourth ventricle	May be cystic	Surgery/radiotherapy	40

CSF, cerebrospinal fluid.

## 12.2 Brain-stem tumours

Brain-stem gliomas, which may vary in their degree of malignancy, form approximately 15% of brain tumours in childhood. Peak incidence 5–9 years of age. Presents with multiple cranial nerve palsies plus long tract signs. Vomiting may be a feature.

- Treatment – radiotherapy
- Survival – poor

## 12.3 Supratentorial tumours

### Cerebral astrocytomas

- Presentation depends on location
- Often leads to seizures
- Low-grade astrocytomas (benign): more common in children
- High-grade astrocytomas: fortunately, more rare

### Ependymomas

- Of ependymomas 30–40% are supratentorial
- These are more malignant than their infratentorial counterparts
- They have a tendency to metastasize and thus prognosis is poor

### Optic gliomas

- One-third prechiasmatic, two-thirds chiasmatic or postchiasmatic
- Generally, these tumours are pilocytic astrocytomas. A quarter occur in the setting of neurofibromatosis type 1
- Clinical presentation – prechiasmatic lesions may present late with proptosis with associated visual loss. Postchiasmatic lesions lead to visual loss
- Treatment – controversial. Often conservative, but surgery and radiotherapy may be indicated

### Craniopharyngioma

Tumour arises from small aggregates of cells that are remnants of the Rathke pouch. The tumour is either suprasellar or suprasellar and intrasellar. Often cystic.

Clinical features are related to the following:

- Endocrine disturbance:
  - Delayed growth
  - Hypothyroidism
  - Diabetes insipidus
- Raised intracranial pressure:
  - Headache
  - Ataxia
- Local features:
  - Visual disturbance (bitemporal hemianopia)
  - Depressed consciousness
  - Vomiting
  - Nystagmus

## Investigations

- Skull X-ray may show erosion of dorsum sellae, also calcification
- MRI will delineate lesion better
- Also, endocrine investigations and visual field mapping.

## Treatment

- Controversial
- Surgery
- Radiotherapy

## 13. NEURO CUTANEOUS SYNDROMES

Neurocutaneous syndromes form a group of unrelated disorders in which skin and neurological features coexist. Most are genetically determined.

### 13.1 Neurofibromatosis

Neurofibromatoses are predominantly inherited disorders.

#### Neurofibromatosis type 1

*NF1* gene localized to chromosome 17q11.2.

#### Diagnostic criteria (two or more are necessary for diagnosis)

- Six or more café-au-lait spots >5 mm in diameter in prepubertal patients and >15 mm in postpubertal patients

- Two or more neurofibromas or one plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more iris hamartomas (Lisch nodules)
- Typical osseous lesions such as sphenoid dysplasia
- First-degree relative affected

## Neurological manifestations

- Macrocephaly
- Learning disability
- Epilepsy
- Optic gliomas

## Neurofibromatosis type 2

*NF2* gene localized to chromosome 22q11.2.

## Diagnostic criteria

- Bilateral nerve VIII neurofibromas
- Unilateral nerve VIII mass in association with any two of the following: meningioma, neurofibroma, schwannoma, juvenile posterior capsular cataracts
- Unilateral nerve VIII tumour or other spinal or brain tumour as above in first-degree relative

## 13.2 Tuberous sclerosis

Dominantly inherited disorder with variable expression. Characterized by skin and CNS abnormalities, although there may be cardiac, renal and bony abnormalities as well. Two mutant genes: *TSC1* (9p34) and *TSC2* (16p).

## Clinical features

- Seizures
- Neurodevelopmental impairment
- Cutaneous manifestations:
  - Adenoma sebaceum
  - Periungual fibromas
  - Hypopigmented patches
  - Shagreen patch
- Retinal hamartomas
- Renal angioliomas
- Cardiac rhabdomyomas



Brain imaging may reveal cortical tubers and subependymal nodules with calcification.

## 13.3 Other neurocutaneous disorders

### Ataxia–telangiectasia

Characterized by conjunctival telangiectasia, progressive cerebellar degeneration and immunological impairment. Multisystem disease with autosomal recessive inheritance. Responsible gene, at least in some families, mapped to chromosome 11q22-23

#### Clinical features

- Progressive ataxia
- Scleral telangiectasia
- Abnormalities of cell-mediated and humoral immunity leading to increased sinopulmonary infections and high incidence of reticuloendothelial malignancies in later life

#### Diagnosis

- Elevated  $\alpha$ -fetoprotein level
- Reduced IgA
- Reduced IgD
- Inversions and translocations involving chromosomes 7 and 14
- Gene mutation analysis

### Sturge–Weber syndrome

Characterized by port wine stain, facial naevus and ipsilateral leptomeningeal angioma, which leads to ischaemic injury to the underlying cerebral cortex, in turn leading to focal seizures, hemiparesis and variable degrees of intellectual deficit.

### Incontinentia pigmenti

- Rare
- Probably inherited as X-linked dominant
- Gene *NEMO*
- Characterized by skin lesions – initially erythematous, papular, vesicular or bullous lesions on trunk and limbs, then pustular lesions, then pigmented lesions
- 30–50% of neurological features:
  - Seizures
  - Encephalopathy
- Eye lesions in 30%

## **Hypomelanosis of Ito**

- Also rare
- Sporadic inheritance
- Hypopigmented areas
- CNS involvement common, including seizures and hemimegalencephaly

## **14. NEUROMETABOLIC DISEASES**

Disorders of intermediary metabolism are a huge group of heterogeneous conditions that have effects of different nature and severity on the nervous system.

### **14.1 Amino and organic acid disorders**

#### **Phenylketonuria**

See [Chapter 16](#).

#### **Branched-chain amino acid disorders**

See [Chapter 16](#).

#### **Glutaric aciduria type I**

- Inborn error of lysine and tryptophan catabolism
- Leads to extrapyramidal syndrome
- Initially, children may develop normally
- May be hypotonic or irritable
- Chronic subdural haematomas may be present
- Acute neurological deterioration occurs
- Brain imaging shows striatal changes

#### **Canavan disease**

- *N*-Acetylaspartic aciduria
- AR (17p13-ter)
- Leads to spongy degeneration of the subcortical white matter
- Progressive neurological impairment
- Death in first decade

## 14.2 Neurotransmitter and urea cycle disorders

### Non-ketotic hyperglycinaemia

- AR
- Glycine accumulates in body fluids
- Neuropathology – identifies poor myelination
- Clinical:
  - Poor respiratory effort at birth
  - Hypotonia
  - Gradual improvement over first week
  - Evolution of myoclonic encephalopathy
- Severe seizure disorder and major developmental delay ensues

### Urea cycle disorders

See [Chapter 16](#).

### OCT deficiency

See [Chapter 16](#).

## 14.3 Mitochondrial disease

### Respiratory chain disorders

Abnormalities of mitochondrial energy production produce a variety of clinical syndromes, many of which have significant neurological features.

### Potential clinical features of respiratory chain disorders

- Lactic acidosis
- Failure to thrive
- Progressive external ophthalmoplegia
- Myopathy
- Seizures
- Dementia
- Movement disorders
- Cardiomyopathy
- Retinopathy
- Deafness

## Specific syndromes

Kearns–Sayre syndrome	Progressive external ophthalmoplegia, heart block, cerebellar dysfunction
MERRF	Myoclonic epilepsy with ragged red fibres (on muscle biopsy)
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
Leigh disease	Subacute necrotizing encephalopathy – hypotonia progressive deterioration in neurological abilities
Alpers disease	Grey matter disease. Seizures are a prominent feature. Liver abnormalities are seen, often late in course of disease

## Abnormalities of fatty acid $\beta$ -oxidation

See [Chapter 16](#).

## 14.4 Abnormalities of copper metabolism

### Wilson disease

- Autosomal recessive
- Excessive accumulation of copper in nervous system and liver due to lack of binding globulin (ceruloplasmin)
- Approximately 30% present with neurological symptoms alone, a third with CNS and liver changes
- Leads to movement disorder which may include dystonia, rigidity and chorea, and may also be characterized by intellectual deterioration and behavioural lability
- Diagnosis by biochemical means
- Treatment – copper chelation therapy with penicillamine

### Menkes disease (kinky hair disease)

- Uncommon X-linked disorder
- Low serum copper and ceruloplasmin
- Gene map to Xq13.3 (*MNK*)

### Clinical

- Onset neonatal period or early infancy
- Hypothermia, poor weight gain
- Hair is sparse, brittle
- Progressive cerebral infarction occurs, leading to seizures and neurological impairment
- Diagnosis confirmed by biochemical or genetic means or by hair examination
- Death in first 2 years

## 14.5 Storage disorders

In these conditions, an enzymatic block leads to accumulation of products of cellular metabolism in the nervous system.

### Sphingolipidoses

These are lysosomal diseases involving disorders of sphingolipid metabolism. Sphingolipids are important components of CNS membranes:

- GM2 gangliosidosis (Tay–Sachs disease): neurodegenerative, onset 3–9 months, startles, seizures, blindness
- Gaucher disease: types 2 and 3 have neurological involvement: hypotonia, progressive deterioration, hepatosplenomegaly
- Niemann–Pick disease: types A and C have neurological involvement leading to progressive deterioration
- Fabry disease: presents with painful hands and feet. May run slow progressive course with renal involvement

### Mucopolysaccharidoses

These are disorders characterized by accumulation of mucopolysaccharides or glycosaminoglycans in lysosomes. There are numerous different types:

- Hurler disease (MPS 1H): characteristic facies, marked dwarfism, corneal clouding, neurological involvement progressive. Hydrocephalus may ensue
- Sanfilippo disease (MPS III): typical mucopolysaccharidosis features may be mild. However, severe neurological involvement with intellectual deterioration and seizures

### Peroxisomal disorders

Peroxisomes are cellular organelles containing proteins and enzymes. Peroxisomal disorders are characterized by accumulation of metabolites normally degraded by peroxisomal enzymes or by decreased amounts of substances normally synthesized by peroxisomes.

### Zellweger syndrome

- Presents in neonatal period
- High forehead, patent fontanelles. Severe hypotonia and poor sucking or swallowing
- Very poor subsequent neurological development
- Often associated with cerebral gyral abnormalities

## **X-linked adrenoleukodystrophy**

- Relatively common disease which involves CNS and adrenals
- Over half present with CNS features. This group present at 4–8 years with cognitive decline and progressive gait disturbance
- Brain imaging shows leukodystrophy
- Levels of very-long-chain fatty acids (VLCFAs) are elevated

## **14.6 Leukodystrophies and other neurodegenerative disorders**

Leukodystrophies are degenerative disorders that affect the white matter of the brain through abnormalities of myelin. In some, the metabolic features are known, in others the diagnosis is based on clinical features.

## **Leukodystrophies**

### **With known metabolic defect**

- Metachromatic leukodystrophy
- Krabbe leukodystrophy
- Adrenal leukodystrophy
- Canavan disease

### **Without recognized metabolic defect**

- Pelizaeus–Merzbacher disease
- Cockayne disease
- Alexander disease
- Leukodystrophy with subcortical cysts
- Leukodystrophy with vanishing white matter

## **Grey matter disorders**

### **Neuronal ceroid–lipofuscinoses (Batten disease)**

These disorders are characterized by storage of pigments that are similar to ceroid and lipofuscin. Although originally thought to be related, genetic analysis has shown them to be separate disorders.

# The neuronal ceroid–lipofuscinoses (NCLs)

Disease	Onset	Clinical features	Course
Infantile NCL	8–18 months	Myoclonus, ataxia, extrapyramidal features, visual impairment slight	Death in first 5 years
Late infantile NCL	18 months–4 years	Epilepsy, marked ataxia, late visual deficit	Death 5–15 years
Juvenile NCL	4–7 years	Visual failure, later dementia	Death 15–30 years
Adult NCL	Adulthood	Slow cognitive decline, normal vision	Slow

## Rett syndrome

Syndrome of dementia, autistic behaviour and motor stereotypes seen in girls.

### Classic clinical features

- Normal perinatal period and normal first year
- Deceleration of head growth from around 9 months
- Loss of neurological skills
- Hand wringing
- Hyperventilation
- Gait apraxia
- May develop scoliosis

Diagnosis was clinical but now by mutation analysis of *MeCP2* gene (Xq28; 80% cases). Mutation analysis has shown that mutations in this gene lead to severe neonatal encephalopathy in boys. At least one more gene implicated (*CDKL5*).

## Angelman syndrome

- Previously known as ‘happy puppet’ syndrome
- Caused by deletion of chromosome 15q11.2-12, which is maternally inherited
- Deletion includes gene for  $\beta_3$  subunit of GABA ( $\gamma$ -aminobutyric acid) receptor

### Clinical features

- Severe learning disability
- Ataxia
- Jerky movements
- Seizures
- Often cheerful demeanour

## 15. HEAD INJURY

It has been estimated that 1 in 10 children have a head injury severe enough to impair consciousness. Boys outnumber girls by 2–3:1. The overall incidence of head injury is 2–3 per 1000 population. Around 5% are severe (Glasgow Coma Scale [GCS] score of 8 or less), 5–10% moderate (GCS 9–12) and 85–90% are minor.

## 15.1 Mild closed head injury

### Clinical features

- Impaired consciousness
- Lethargy
- Crying
- Vomiting
- Ataxia

Develops immediately or within 6–8 hours of injury. There is usually complete resolution of symptoms within 24 hours of the injury.

## 15.2 Severe closed head injury

Characterized by major loss of consciousness which is deeper and persists longer than in milder head injury. The greatest neurological deficit usually occurs immediately after the injury. Injuries may be the result of:

- Primary trauma to brain
- Secondary changes due to inflammation and ischaemia

Paediatric Glasgow Coma Scale		
Eye opening (E)	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response (V)	Oriented	5
	Words	4
	Inappropriate sounds	3
	Vocalization	3
	Cries	2
	None	1
	Obeys command	6



	Localises pain	5
Best motor response (M)	Withdraws to pain	4
	Abnormal flexion to pain	3
	Abnormal extension to pain	2
	None	1

### Clinical assessment

- Level of consciousness
- Respiratory pattern
- Pupil size and reaction
- Brain-stem signs
- Leakage of CSF
- Focal signs
- Consider potential of cervical spine fracture

### Management

- Airway, breathing, circulation
- X-ray of cervical spine
- Assess intracranial pressure
- CT scan
- Fluid restriction
- After first 4–5 days – supportive care

### Late complications

- Learning disability (global and specific)
- Behavioural disturbance
- Motor deficits
- Post-traumatic epilepsy
- Headaches

## 15.3 Non-accidental head injury

The incidence of non-accidental head injury is unknown but most estimates almost certainly under-diagnose the problem. Non-accidental head injury may include blunt trauma, sometimes leading to skull fracture, and the so-called shaken (or shaken-impact) baby syndrome.

### Clinical features of ‘shaken baby syndrome’

- Peak incidence 5 months of age

- History inconsistent with severity of injury
- Baby presents shocked, possibly apnoeic, following apparent sudden spontaneous collapse at home
- Impaired consciousness
- Shocked
- Irregular breathing
- Retinal haemorrhages
- Possible bruising on arms or trunk
- Brain imaging identifies acute and/or chronic intracranial bleeding with brain swelling
- There may be signs of other non-accidental injury

### **Mechanism**

- Unclear
- Cerebral parenchyma may be damaged by blunt trauma
- Recent evidence suggests brain-stem injury leading to apnoea and ischaemic injury

### **Prognosis**

- Non-accidental head injury may lead to death
- Prognosis for neurological recovery guarded

## **16. SPECIFIC NEUROLOGICAL LESIONS**

### **16.1 Cranial nerve lesions**

#### **Facial nerve paralysis**

Symptoms and signs will depend on location of lesion in the course of the nerve with potential abnormalities of taste, lacrimation and salivation as well as hyperacusis.

#### **Congenital facial paralysis**

- May be due to birth trauma or prenatal compression
- May also be non-traumatic due to anomalies of nerve and nerve cell body

#### **Moebius syndrome**

- Bilateral facial paralysis with bilateral abducens paralysis
- Other lower cranial nerves may be affected
- Up to a quarter have learning disability

#### **Acquired facial palsy (Bell palsy)**

- Acute, usually idiopathic, paralysis which is unilateral
- Weakness maximal for 2–4 weeks
- Complete recovery is usual
- Steroids often given, but no evidence to support their use

## **Other facial paralyses**

- Lyme disease
- Otitis media/mastoiditis
- Hypertension

## **Lower cranial nerve palsies (VII–XII)**

- Congenital: often present in Chiari I and II malformations

## **16.2 Disorders of eye movement**

### **Acquired ophthalmoplegia**

#### **Nerve III palsy**

- Common
- Most frequently due to closed head trauma, infections and tumours

#### **Nerve IV palsy**

- Traumatic

#### **Nerve VI palsy**

Due to raised intracranial pressure:

- Tumours
- Benign intracranial hypertension

### **Congenital ophthalmoplegia**

- Can affect all the above nerves

### **Nystagmus**

- Involuntary, rhythmic, conjugate, oscillatory movements of the eyes that may occur in any plane
- Results from dysfunction of complex mechanisms that maintain ocular fixation

Type	Cause
Pendular	Congenital Acquired – disease of brain stem/cerebellum
Horizontal jerk:	
Vestibular	End-organ
Gaze evoked	Posterior fossa
Rotary	Vestibular or medullary lesions

## Differential diagnosis

- Roving eye movements of blind children
- Opsoclonus

## 16.3 Unequal pupils

- May be due to physiological anisocoria
- Establish which pupil is abnormal
- Ptosis and large pupil – nerve III palsy
- Ptosis and constricted pupil – Horner syndrome
- Extremely important in unconscious patient (much more so than establishment of papilloedema, for example)

## 17. NEUROLOGICAL INVESTIGATIONS

### 17.1 Electroencephalography

The EEG allows an assessment of changes in cortical function. Electrodes applied to the scalp allow the cortical action potential between two electrodes to be amplified and displayed. The quality of the normal EEG will depend upon:

- Age of the patient
- Whether the patient is awake or asleep

### Uses

- Investigation of patients with seizures
- Detection of cerebral dysfunction
- Evaluation of depressed consciousness
- Investigation of neurodegenerative disorders

### Typical EEG appearances

## **Epilepsies**

- Three cycle/s spike and wave in typical absences ('petit mal')
- Four cycle/s spike and wave and poly spike and wave bursts in juvenile myoclonic epilepsy
- Clusters of high-amplitude spike and wave complexes in one or both rolandic areas in benign focal epilepsy with rolandic spikes

## **Epileptic encephalopathies**

- High-voltage chaotic slow waves and spike-and-sharp waves in hypsarrhythmia
- Spike and waves in absence of seizures and loss of language skills in Landau–Kleffner syndrome
- Slow spike–wave discharges at 1.5–2.5 cycles/s in Lennox–Gastaut syndrome

## **Undiagnosed neurological illness**

- Burst suppression in asphyxia, early myoclonic epilepsy, glycine encephalopathy
- Slowing of background in encephalopathies generally
- Focal slowing may indicate structural lesions such as cerebral abscess
- Focal flattening may indicate subdural haemorrhage or effusion
- Diffuse moderate amplitude fast beater activity is the result of some drug intoxications

## **Suspect cerebral malformation or learning disability**

- High-voltage activity in the  $\alpha$  frequency or lower part of  $\beta$  characteristic of lissencephaly or pachygyria
- High-voltage posterior spike and wave accentuated by passive eye closure is a feature of Angelman syndrome
- Trains of spikes or sharp waves, at first in sleep, with poorly organized background activity develop in Rett syndrome

## **Suspect neurodegenerative disorder**

- Stereotyped high-voltage polyphasic complexes repeated every few seconds and often associated with transient reduction in tone – subacute sclerosing panencephalitis
- Progressive reduction in EEG amplitude after infancy is typical of infantile neuronal ceroid lipofuscinosis
- High-voltage posterior complexes induced by slow stroboscopic activation at less than 0.5 cycles/s is typical of late infantile neuronal ceroid lipofuscinosis
- $\beta$  activity of moderate amplitude develops after 2 years in infantile neuraxonal dystrophy
- Multiple spikes superimposed on lateralized large slow waves suggest progressive neuronal degeneration of childhood, and predict later hepatic involvement

## **17.2 Evoked potentials**

Used to assess the function of auditory, visual and somatosensory pathways.

## **Auditory brain-stem-evoked potentials**

- Assessment of peripheral hearing in infants and young children

## **Visual evoked potentials**

- Detection of disease in anterior visual pathway

## **Electroretinogram**

- Measures response of retina to repeated light flashes
- Used in investigation of low vision and in neurological regression

## **Somatosensory evoked potentials**

- Diagnosis of spinal cord disease
- Intraoperative monitoring

## **17.3 Peripheral neurophysiology**

Measurement of peripheral nerve conduction allows assessment of the function of the motor unit – the anterior horn cell, peripheral axon and innervated muscle.

Nerve conduction studies allow measurement of:

- Motor nerve conduction velocity – reduced in demyelination
- Amplitude of action potential – reduced in axonal neuropathies
- Sensory nerve conduction velocity – reduced in Friedreich ataxia, for example

## **Electromyography**

- Denervation: shorter and lower voltage action potentials – later giant potentials
- Myopathic change: reduced action potentials

## **17.4 Brain imaging**

### **Computed tomography**

Useful in:

- Initial evaluation of coma
- Trauma
- Calcification

## **Magnetic resonance imaging**

Useful in:

- Detection of parenchymal lesions, especially white matter lesions
- Posterior fossa lesions

## **17.5 Lumbar puncture**

Useful in diagnosis of:

- Infection
- Demyelinating diseases
- Subarachnoid haemorrhage
- Benign intracranial hypertension (measure pressure)

## **18. FURTHER READING**

Aicardi J (2009). *Diseases of the Nervous System in Childhood. Clinics in Developmental Medicine*, 3rd edn. London: MacKeith Press.

King MD, Stephenson JBP (2009). *A Handbook of Neurological Investigations in Children*. London: MacKeith Press

Patten J (1995). *Neurological Differential Diagnosis*, 2nd edn. New York: Springer Verlag.

Volpe J (2008). *Neurology of the Newborn*, 5th edn. Philadelphia, PA: WB Saunders.

---

# Chapter 20

## Ophthalmology

*Ken K Nischal*

---

## CONTENTS

### **1. Basic anatomy of the eye**

- [1.1 Orbits](#)
- [1.2 Extraocular muscles](#)
- [1.3 The globe](#)

### **2. Eyelid abnormalities**

- [2.1 Congenital eyelid abnormalities](#)
- [2.2 Infections and inflammation of the lids](#)
- [2.3 Haemangiomas](#)
- [2.4 Ptosis](#)

### **3. Lacrimal system disorders**

- [3.1 The watering eye \(lacrimation and epiphora\)](#)
- [3.2 The dry eye](#)

### **4. Proptosis**

- [4.1 Orbital infections](#)
- [4.2 Orbital tumours](#)

### **5. Eye movement and strabismus**

- [5.1 Squint \(strabismus\)](#)
- [5.2 Nystagmus](#)

### **6. Diseases of the conjunctiva**

- [6.1 Conjunctivitis](#)
- [6.2 Other conjunctival disorders](#)



## **7. Diseases of the cornea**

## **8. Diseases of the sclera**

## **9. Photophobia**

## **10. Causes of a painful red eye**

## **11. Uveal tract disorders (iris, ciliary bodies and choroid)**

[11.1 Aniridia](#)

[11.2 Albinism](#)

[11.3 Brushfield spots](#)

[11.4 Heterochromia iridis](#)

[11.5 Coloboma](#)

[11.6 Inflammation of the iris](#)

## **12. Abnormalities of the pupil**

## **13. Childhood glaucoma**

## **14. Lens disorders**

[14.1 Developmental anomalies](#)

[14.2 Dislocated lens \(ectopia lentis\)](#)

[14.3 Cataract](#)

## **15. Retinal disorders**

## **16. Infections and the retina**

## **17. Optic nerve disorders**

[17.1 Papilloedema](#)

[17.2 Optic atrophy](#)

## **18. Metabolic diseases and the eye**

## **19. Miscellaneous disorders**

## **20. Ocular trauma**

## **21. Acquired visual loss**

## **22. Visual assessment and refractive errors**

[22.1 Visual assessment](#)

[22.2 Refractive errors](#)

## **[23. Ophthalmological investigations](#)**

## **[24. The visually impaired child](#)**

## **[25. Further reading](#)**

# Ophthalmology

## 1. BASIC ANATOMY OF THE EYE

### 1.1 Orbits

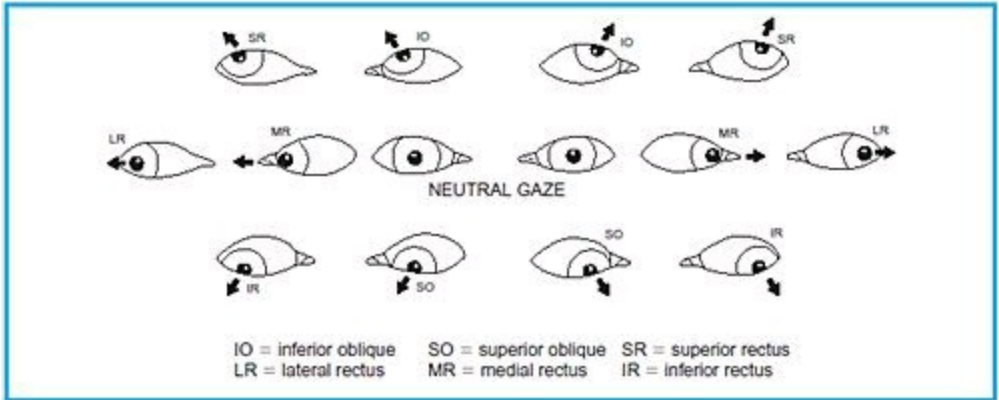
The orbits are related to the frontal sinus above, the maxillary sinus below, and the ethmoid and sphenoid sinuses medially. The orbit houses the eyeball, which occupies only one-fifth of the space, fat and muscle, accounting for the bulk of the remainder. Other orbital structures include the lacrimal glands, attendant arteries, veins and nerves.

### 1.2 Extraocular muscles

Six extraocular muscles control the movement of each eye – four rectus and two oblique muscles.

Muscle	Nerve supply	Primary action	Secondary action
Lateral rectus nerve	VI (abducens)	Abduction	None
Medial rectus	III (oculomotor)	Adduction	None
Superior rectus	III	Elevation	Adduction, intorsion
Inferior rectus	III	Depression	Adduction, extorsion
Superior oblique	IV (trochlear)	Depression	Intorsion, abduction
Inferior oblique	III	Elevation	Extorsion, abduction

Note that an easy way to remember extraocular muscles innervations is L6 SO4/3 (where L = lateral rectus, innervated by sixth nerve, SO = superior oblique innervated by fourth nerve, and all the rest innervated by third nerve).



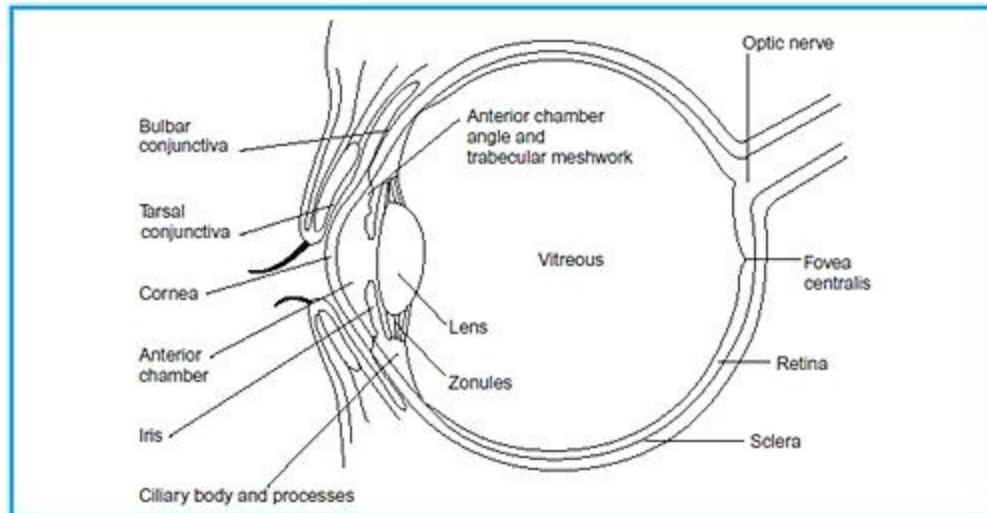
The action of the external ocular muscles with the patient confronting the examiner.

## 1.3 The globe

### The eyelid

Protective cover for the eyeball.

### The eyeball



The eyeball.

The most important contents are as follows.

#### Cornea

A transparent avascular tissue inserted into the sclera at the limbus, functioning as a protective membrane and a 'window' through which light rays pass en route to the retina. Sensory innervation is supplied by the first division of the trigeminal nerve. Transparency of the cornea is due to its uniform structure, avascularity and the state of relative dehydration of the corneal tissues, which is maintained by the active bicarbonate pump of the endothelium.

#### Conjunctiva

Thin, transparent mucous membrane that covers the posterior surface of the lids (the palpebral conjunctiva) and the anterior surface of the sclera (the bulbar conjunctiva).

#### The sclera

The fibrous outer protective coating of the eye. In the infant, the sclera is thin and translucent with a bluish tinge.

#### Uveal tract

Consists of iris, ciliary body and choroid, each of which has a rich vascular supply and pigment. The choroid's vascular supply provides nutrition for 65% of the outer retinal layers.

### **Anterior chamber**

Fluid-filled space between the cornea and the iris diaphragm. The aqueous fluid is secreted by the ciliary body, reaches the anterior chamber by passing through the pupillary space and drains via the trabecular meshwork in the periphery of the anterior chamber into the venous circulation. The aqueous humour provides nutrition for the corneal endothelial surface.

### **Lens**

This lies posterior to the iris and anterior to the vitreous humour, suspended by zonular fibres from the ciliary body. Anterior to the lens is the aqueous humour, posterior to it the vitreous. The lens of the newborn infant is more nearly spherical than that of the adult, with greater refractive power helping to compensate for the relative shortness of the young eye.

### **Vitreous**

A transparent gelatinous structure that fills the posterior four-fifths of the globe. It is firmly attached to the pars plana anteriorly and has a loose attachment to the retina and optic nerve posteriorly. The vitreous is about 99% water.

### **The retina**

During the first 2–3 months of life, children develop the ability to focus images at any range. The retina contains the sensory receptors: the rods and cones. The fovea centralis is the centre of the macula and it has the greatest concentration of cones, and therefore has the greatest potential for visual acuity. Light falling on the fovea and peripheral retina is converted into nerve impulses by the rods and cones. Nerve fibres emanate from the ganglion cell layer of the retina, coalesce to form the optic nerve and synapse in the lateral geniculate body. Fibres from the temporal retina travel without crossing at the chiasma to the ipsilateral visual cortex. Nerve fibres from the nasal retina will decussate at the chiasma and are directed towards the contralateral visual cortex. The decussation of nerve fibres causes portions of each retina to image a different part of the visual field.

## **2. EYELID ABNORMALITIES**

### **2.1 Congenital eyelid abnormalities**

#### **Cryptophthalmos**

A rare condition in which the skin is continuous over the eyeball with an absence of eyelids.

#### **Coloboma**

This is clefting (a defect) of the eyelid, which may occur as an isolated anomaly or in association with other clefting abnormalities or first arch syndromes (Goldenhar and first arch syndrome). Management depends on the size of the cleft and the other associated signs. For larger clefts urgent reconstruction of the lid is necessary. Ocular exposure can be controlled with lubricants.

## **Ablepharon**

Congenital absence of the eyelids; exposure keratopathy is a serious risk to vision.

## **Ankyloblepharon**

Partial or complete fusion of the eyelid margins.

## **Ectropion**

Congenital ectropion is an outward rotation of the eyelid margin present at birth. Associated with other conditions such as ichthyosis, which may present as collodion baby at birth. It may also be associated with Down syndrome.

Management may be initially conservative using lubrication. Surgical intervention is indicated for exposure keratitis and may include skin grafting.

## **Entropion**

Turning inward of the lid margin with lashes rubbing against the conjunctiva.

## **Epicanthus**

Epicanthal folds are folds of skin that extend from the upper eyelid towards the medial canthus. The epicanthus may give rise to a false appearance of strabismus (pseudosquint).

## **Telecanthus**

There is an increased width between the medial canthi with normal interpupillary distance.

## **Hypertelorism**

Increased intralobular distance.

## **Hypotelorism**

Reduced intralobular distance.

## **Blepharophimosis**

Small eyelids. May be part of the blepharophimosis syndrome.

## **2.2 Infections and inflammations of the lids**

# Stye

Infected eyelash follicle.

## Chalazion (meibomian cysts)

A chronic granulomatous inflammation of the meibomian gland which results from obstruction of the gland duct. Usually occurs away from the lid border as a painless hard nodule. Treatment involves the use of warm compresses to help drainage of the lipid material. Small chalazia may resolve spontaneously, but incision and drainage may be necessary for persistent ones. Recurrent chalazia may be a sign of chronic meibomian gland dysfunction and needs referral to a paediatric ophthalmologist

## 2.3 Haemangiomas

Capillary haemangiomas can affect either lids and are usually noticed soon after birth as reddish discolorations of the eyelid which progressively develop into an enlarging mass.. Complete resolution may take up to the age of 8 years. If large enough to interfere with the visual axis, intervention with steroids and/or other modalities such as laser therapy may be required. More recently systemic beta blockers are the favoured treatment.

## 2.4 Ptosis

Drooping of the upper lid, which may be unilateral or bilateral, congenital or acquired. The most common cause of ptosis in childhood is simple congenital ptosis, which is due to a dystrophy of the levator palpebrae superioris muscle.

### Causes of ptosis

- **Congenital ptosis**
  - Dystrophic, e.g. simple congenital ptosis
  - Non-dystrophic: aponeurotic defect, e.g. neurogenic, mechanical
- **Acquired ptosis**
  - Aponeurotic (trauma or oedema)
  - Lid inflammation (trauma, oedema)
  - Neurogenic (e.g. third nerve palsy, Horner syndrome and Marcus Gunn jaw-winking syndrome)
  - Myogenic (e.g. progressive external ophthalmoplegia, ocular myopathies and myasthenia gravis)
  - Mechanical (e.g. lid tumours and lacerations)
  - Infections (e.g. encephalitis and botulism)
  - Syndromes (e.g. Sturge–Weber syndrome and neurofibromatosis)
  - Drugs (e.g. vincristine)

# Horner syndrome

This is caused by sympathetic denervation. May be congenital or acquired.

## Features

- Ptosis (partial)
- Miosis (pupil constriction)
- Enophthalmus
- Anhidrosis (ipsilateral)
- Heterochromia iridis (congenital type)
- Normal direct and consensual reflex to light

**Congenital** may be caused by obstetric trauma, with cervical vertebral anomalies, congenital tumours and infection such as varicella syndrome.

**Acquired** may be caused by trauma, surgery or tumours such as neuroblastoma.

# Marcus Gunn jaw-winking syndrome

This is due to an abnormal synkinesis between the levator and the lateral pterygoid muscle. The affected eyelid is usually ptotic, but elevates when the jaws open and deviates to the contralateral side. To perform the test, look for ptosis when the jaw is closed, then ask the child to open his or her mouth wide; this will result in rising of the ptotic upper lid.

# Myasthenia gravis

This is rare in children. However, the presence or absence of fatigability should be determined. The Tensilon (edrophonium chloride) test should be undertaken in a clinically controlled environment with resuscitative equipment because it may cause cardiac arrhythmias. A small dose of intravenous Tensilon should be given and then 30 seconds later, if no adverse effect is noted, a larger volume can be given. Results are seen within 1 minute and wear off quickly. The child should be on no drugs that inhibit acetylcholinesterase.

The use of the 'ice-pack test' is controversial in the definitive diagnosis of myasthenia gravis.

# Treatment of ptosis

Ptosis of sufficient degree to interfere with vision requires early correction to prevent permanent loss of vision (amblyopia). Surgical treatment such as levator resection is an option. In severe congenital ptosis the eyelid can be suspended from the brow and elevated by the frontalis muscle.

## 3. LACRIMAL SYSTEM DISORDERS



The lacrimal system's function is to produce and remove tears.

## **Congenital nasolacrimal sac dilatation (mucocele or dacryocystocele)**

This presents shortly after birth as a bluish mass in the region of the nasolacrimal sac. Treatment varies from conservative massage to probing within a few days.

## **Dacryocystitis**

This may be caused by bacterial infection of the nasolacrimal sac associated with nasolacrimal duct obstruction. It presents with swelling of the nasolacrimal sac region and cellulitis of the surrounding tissues.

## **Stenosis or obstruction of the nasolacrimal duct**

This may occur in 30% of newborn infants. Signs include mucopurulent discharge or tearing which may start 3–5 weeks later. Gentle pressure over the nasolacrimal sac expresses tears and mucopurulent material from the sac. Spontaneous resolution is common, but probing of the nasolacrimal duct may be required.

## **3.1 The watering eye (lacrimation and epiphora)**

Lacrimation means excessive secretion of tears, e.g. in crying, whereas epiphora means watering of the eyes, i.e. overflow because of inadequate drainage. The newborn baby does not usually shed tears during crying for the first 4–6 weeks of age.

### **Causes of epiphora**

- Blocked nasolacrimal system
- Congenital glaucoma
- Acquired foreign body
- Keratitis and conjunctivitis
- Facial palsy
- Chronic blepharitis
- Migraine
- Contact lens
- Drugs (e.g. maternal heroin addiction)
- Congenital glaucoma (epiphora together with photophobia may herald congenital glaucoma)
- Non-patent nasolacrimal system

## **3.2 The dry eye**

The child with a dry eye rarely complains that it is dry, but does complain of a burning sensation. It is a relatively uncommon problem.

## Causes of dry eye

- **Tear mucin deficiency**, e.g. vitamin A deficiency (xerophthalmia), trachoma, burns and Stevens–Johnson syndrome
- **Tear lipid-layer deficiency**
- **Aqueous tear-deficiency**, keratoconjunctivitis sicca
- **Congenital alacrima**
- **Ectodermal dysplasia** – dry skin, the anhidrotic type – absence of sweat and sebaceous glands, poor hair formation and abnormalities of nails and teeth
- **Familial dysautonomia** (Reilly–Day syndrome – autosomal recessive almost exclusively in children of Ashkenazi Jewish origin): emotional lability, paroxysmal hypertension, sweating, cold hands and feet, and blotchy skin
- **Sjögren syndrome** – uncommon in childhood, arthritis, dryness of mouth and other mucous membrane and dry eyes, tendency to bronchitis and pneumonia with pulmonary disease
- **Drug induced**

## Treatment of dry eyes

Treatment is not always satisfactory. It generally involves avoidance of dry atmosphere (e.g. excessive central heating), active use of sleeping-room humidification and increasing humidity by the use of glasses or goggles. The mainstay of treatment is artificial tears.

## 4. PROPTOSIS

This is defined as abnormal protrusion of the eyeball. Proptosis (exophthalmos) is most easily appreciated when the examiner looks at the patient’s eyes from above the top of the head. It may be unilateral or bilateral (due to pressure from behind) or false (due to prominent eyeball).

## Causes of proptosis

- Infection such as orbital cellulitis and ethmoiditis
- Cavernous sinus thrombosis
- Tumours:
  - Neuroblastoma
  - Retinoblastoma
  - Optic nerve glioma
  - Histiocytosis
  - Angioma/haemangioma
  - Rhabdomyosarcoma
- Thyrotoxicosis

- Craniosynostoses
- Dermoid
- Orbital encephalocele
- Mucocele of the paranasal sinus
- Coagulation disorders (haemorrhage) and other orbital and frontal bone osteomyelitis

## Investigations

In all cases of proptosis the clinician should determine whether this is bilateral or unilateral, acquired or congenital, rapidly or slowly progressing if acquired.

All cases of rapidly progressing proptosis need urgent orbital imaging (computed tomography [CT] or magnetic resonance imaging [MRI]). A CT scan is preferred despite the exposure to X-rays, because the orbital bony walls are better seen and often destruction of one or more of these may indicate an aggressive neoplastic condition. In cases of slowly progressive or position-dependent proptosis, MRI with contrast is helpful to exclude or confirm a haemangioma. If a vascular lesion is suspected then orbital Doppler ultrasonography is also needed.

Abdominal examination for involvement may occur in histiocytosis X (although proptosis is usually seen in eosinophilic granuloma which is often localized).

## 4.1 Orbital infections

### Preseptal cellulitis

This occurs when the infection is anterior to the orbital septum. It is more common than orbital cellulitis. Causes include eyelid trauma, extraocular infection and upper respiratory tract infection (URTI). Usually unilateral, and no associated proptosis. The causative organism varies with age, being streptococcal pneumonia and staphylococcal abscess in the neonatal period and *Haemophilus influenzae* in later infancy.

**Treatment:** antibiotic and treatment of the underlying condition, e.g. dacryocystitis.

### Orbital cellulitis

An uncommon but serious infection, which may give rise to ocular and septic intracranial complications. More frequent in children older than 5 years. Over 90% of cases occur secondary to sinusitis, usually of the ethmoid sinus. *H. influenzae* type b is the most common organism during infancy, but other common organisms are staphylococci, causing abscesses, and *Streptococcus pneumoniae*.

**Presentation:** usually with painful red eye and lid oedema; conjunctival chemosis, injection and axial proptosis with limitation of eye movement. The child is usually pyrexial. Urgent treatment is needed to avoid cavernous sinus thrombosis.

**Treatment:** admission to a hospital. Investigations (blood culture, CT scan and sinus radiograph). Ear, nose and throat (ENT) assessment. Systemic antibiotics initially given intravenously.

## 4.2 Orbital tumours

The most common primary orbital malignancy in childhood is rhabdomyosarcoma, which usually occurs between the age of 7 and 8 years and presents with progressive unilateral proptosis. Secondary metastases (especially neuroblastoma) present with an abrupt onset of proptosis and ecchymosis which may be bilateral.

Proptosis may be secondary to optic nerve glioma. Dermoid and epidermoid cyst are relatively uncommon. The most common site of a dermoid cyst is the lateral brow area.

Neuroblastoma is usually associated with ecchymosis and a thorough systemic examination is warranted if seen.

## 5. EYE MOVEMENT AND STRABISMUS

### 5.1 Squint (strabismus)

**Definition:** misalignment of the visual axis.

**Prevalence:** approximately 4% of children younger than 6 years of age have strabismus. Some 25% of children with childhood-onset strabismus have either a parent or a sibling with strabismus.

**Pseudostrabismus:** this is seen in infants with prominent epicanthal folds, closely placed eyes and flat nasal bridges. Observation of symmetrical corneal light reflexes or cover testing will confirm or exclude the presence of true deviation.

### Classification of squint

- Heterophoria (latent squint)
- Concomitant squint (non-paralytic strabismus):
- Esotropia (convergent squint) – an inward deviation of the eyes (most common type of squint)
- Exotropia (divergent squint) – an outward deviation of the eyes
- Inconcomitant squint (paralytic strabismus)

### Causes of strabismus

- Congenital
- Cranial nerve palsy and developmental abnormalities
- Möbius syndrome (association of congenital bilateral facial palsy and bilateral abducens palsy):

facial palsies usually spare lower face. May be inherited, usually sporadic

- Duane syndrome: congenital hypoplasia of the nerve VI nucleus. Nerve III compensates by innervating lateral rectus muscle, resulting in failure of abduction on lateral gaze and globe retraction (palpebral fissure narrows) on adduction; 15–20% are bilateral. Usually sporadic. Associations include Goldenhar syndrome, hemivertebra and Marcus Gunn jaw winking
- Brown syndrome (failure of elevation of the eye, maximal in adduction): usually congenital developmental anomaly of the superior oblique tendon. Occasionally acquired as a result of trauma or surgery. Present with abnormal head posture, elevation of the chin and turning the head away from the affected eye in order to acquire binocular vision. May resolve spontaneously, but surgery may be indicated, especially when deterioration takes place
- Congenital ptosis and myasthenia gravis (rare):
  - Acquired:
    - cranial nerve palsies
    - nerve III lesion: complete ptosis, diplopia, eye turned ‘down and out’ (unopposed lateral rectus and superior oblique muscles) and failure of pupil to react to light or accommodation
    - nerve IV palsy: diplopia and failure of inferior – lateral gaze (failure of the superior oblique muscle)
    - nerve VI palsy: diplopia and medial gaze (failure of lateral rectus muscle)
- Neuromuscular disease: myopathy, myasthenia gravis and botulism.
- Infections of the orbit or brain: raised intracranial pressure, e.g. tumour and post-infectious (Miller–Fisher syndrome, a variant of Guillain–Barré syndrome)
  - Brain-stem disorders

## Causes of esotropia (convergent squint)

- Refractory error – hypermetropia
- Cataract
- Lesions of the optic nerve or macular
- High refractive error or asymmetrical refractive errors

## Causes of exotropia (divergent squint)

- Intermittent exotropia is common, and is most evident when the child is tired and fixating on a distant object. Constant exotropia may be congenital or caused by poor vision in the outward turning eye

## Heterotropia

This is a constant ocular malalignment. Children with heterotropia suppress the image of one eye to avoid diplopia. Amblyopia will result in the suppressed eye when one eye is used for fixation. Early diagnostic assessment is needed to prevent permanent loss of vision in one eye. A fixed squint is commonly found in cerebral palsy, microcephaly and hydrocephalus. The rapid development of a squint may suggest the possibility of a cerebral tumour.

# Amblyopia

This is a term used to describe severe impairment of vision as a result of significant interruption of normal visual development.

## Causes of amblyopia

- Strabismus is by far the most common cause
- Anisometropia – refractive state of one eye significantly different from the other eye
- Ametropia – high refractive error in both eyes and then deprivation – as a result of opacity within the visual axis such as cataract. Usually unilateral. Strabismus is the most common cause

## Treatment

This depends on the cause. If significant refractive error exists, then optical correction must be made early. Intervention is rarely effective after 8 years of age. Opacities such as cataract should be treated. If strabismus is present then amblyopia must first be reversed with occlusion therapy before surgical treatment.

## Assessment of squint

It is important to check that the child can see with each eye first, and that each eye moves to a normal range when tested separately (to exclude paralytic squint). There is a latent tendency for ocular misalignment under certain conditions, e.g. fatigue, illness and stress.

It is important to remember that squints do not cause imbalance in children unless they are acquired and causing double vision. These must be urgently referred to the ophthalmologist. Congenital or early onset squints do not usually cause diplopia. They must be referred to allow gain of binocularity as soon as possible.

## Facial appearance

Squint may be obvious on general inspection; however, a broad epicanthic fold can give the appearance of a convergent squint. An abnormal head posture may be a sign of a squint.

## Corneal reflections

These should be identical in position in both eyes. Using a penlight held about 30 cm (12 inches) from the eye.

## Ocular movements

These should be tested in both horizontal and vertical axes using a small fixation object. Limitation of movement in one direction suggests a paralytic squint.

The cover test consists of three parts:

- Cover test
- Uncover test
- Alternate cover test

In all three tests the patient looks intently at a target, which may be in any direction of gaze, distant or near. In each test, each eye is encouraged to take up fixation separately while the other is covered.

### **Cover test**

As the examiner observes one eye, a cover is placed in front of the other eye so as to block its view of the target. If the observed eye moves to take up fixation, it clearly is not fixating the target, and manifest deviation (strabismus) is present.

### **Uncover test**

As the cover is removed from the eye after the cover test, the eye emerging from under cover is observed. If the position of the eye changes, interruption of binocular vision has allowed it to deviate, and heterophoria (latent squint) is present.

### **Alternate cover test**

The cover is alternately placed in front of one eye and then the other. This tends to break up the control of heterophoria that may last through a single cover–uncover cycle. This test shows the total deviation of constant squint plus latent squint.

## **Management of squint**

Any squint after the age of 4 months should be referred to an ophthalmologist. A fixed squint (a large deviation with little movement of the eyes) should be referred early because it is always abnormal.

The following four approaches are possible:

1. Occlusion (occlusion of the good eye encourages the use of squinting eye and the development of fixation)
2. Correction of refractory errors: spectacles
3. Involvement of orthoptist and paediatric ophthalmologist/strabismologist as with amblyopia
4. Surgery is necessary to gain binocular function and/or to improve social interaction with peers

## **5.2 Nystagmus**

This is defined as involuntary rhythmic movement of one or both eyes about one or more axis. Broadly divided into three main categories:

1. Nystagmus secondary to a visual deficit
2. Nystagmus secondary to intracranial lesions and drug toxicity

### 3. Congenital benign idiopathic nystagmus

Each cycle of nystagmus oscillation may have a slow phase and a fast component, in which case it is called ‘jerk nystagmus’. Oscillations without a quick phase are called ‘pendular’.

### Other classifications

- Physiological
- Congenital (appear before the age of 6 months): blindness, familial and idiopathic

### Acquired nystagmus

(Usually after the age of 6 months)

- Spasmus nutans
- Ictal nystagmus (with epilepsy)
- Cerebellar disease
- Spinocerebellar degeneration
- Vestibular
- Drugs, e.g. carbamazepine
- Optic nerve and chiasma tumour (rare)

### Spasmus nutans

Acquired nystagmus is characterized by the triad of pendular nystagmus, head nodding and torticollis. The nystagmus is fine, rapid, horizontal and pendular. Signs usually develop within the first 2 years of life, but the components of the triad may develop at various times.

It is often benign and self-limiting, resolving in a few months but sometimes years. Some children with brain tumours may exhibit signs resembling those of spasmus nutans. Therefore careful assessment and neuroimaging may be required.

Cerebellar nystagmus is the most important sign to recognize. It is usually horizontal and worsens on looking to the side of the lesion, with the first component directed towards the side of the lesion.

Vestibular nystagmus differs in that the slow phase is directed towards the side of the lesion due to disorders of labyrinth, vestibular system, vestibular nuclei of the brain stem or cerebellum.

### Vertical nystagmus

This is usually due to lesions of the brain stem at the pontomedullary junction (roughly at the foramen magnum), e.g. achondroplasia or Arnold–Chiari malformations. However, early onset cone dystrophies may also present with vertical nystagmus in children. An ERG is needed to exclude this diagnosis and a history of photophobia is also noted.

### Clinical test for nystagmus



Ask the child to look at a flashlight or a toy held in front of the eye. Ask the child to follow the object as you move it quickly, first to one side, then to the other, and also up and down. Rotating the child induces a vestibular nystagmus; on stopping the character of the original nystagmus should return immediately. If it does not and the amplitude or nature of the nystagmus changes (i.e. horizontal to multiplanar) then the possibility of acquired neurological disease should be considered and the child referred.

## 6. DISEASES OF THE CONJUNCTIVA

### 6.1 Conjunctivitis

This is the most common conjunctival disease. It may be bacterial, viral, allergic, toxic or part of a systemic disease.

#### **Bacterial conjunctivitis**

##### **Neonatal conjunctivitis (previously referred to as ophthalmia neonatorum)**

A common problem with an incidence as high as 7–19% of all newborns in the first month of life. Usually bacterial.

##### **Gonococcal conjunctivitis**

A hyperacute bacterial conjunctivitis with thick purulent discharge and lid oedema caused by *Neisseria gonorrhoeae* (Gram negative). Incubation period 2–5 days. Requires prompt treatment because untreated it can rapidly progress to corneal perforation and potentially blinding. Treatment with systemic antibiotics, usually third-generation cephalosporin for 7 days because of the increasing resistance, together with topical irrigation of the eyes.

##### ***Chlamydia trachomatis***

This is the most common organism causing ophthalmia neonatorum in the USA. Infection may vary from mild inflammation to severe swelling of the lids and copious purulent discharge. Potentially blinding. Treatment is with tetracycline ointment for 2 months and systemic erythromycin.

##### ***Pseudomonas aeruginosa***

Usually acquired in the nursery, characterized by the appearance of oedema on days 5–18, erythema of the eyelids and purulent discharge. Progression to endophthalmitis and septic shock can occur. Treatment is with systemic antibiotics. *Pseudomonas aeruginosa* ulcers may frequently affect young children and contact lens wearers.

#### **Other bacterial infections in infants and older children**

Staphylococci and *Haemophilus* spp. and *Strep. pneumococcus* all cause purulent conjunctivitis and need treatment with systemic antibiotics.

#### **Allergic conjunctivitis**

Occurs as a hypersensitivity to dust, pollen, animal dander and other airborne allergens; it is characterized by tearing and itching with conjunctival oedema. Usually seasonal. Topical anti-mast-cell stabilizer or topical steroids are helpful. Systemic antihistamines may be required.

### **Vernal conjunctivitis**

Usually occurs later in the prepubertal period. Atopy may be a factor. Extreme itching is the usual complaint with redness, watering of the eye and lid swelling. It results in cobble-stone appearance of the palpebral conjunctiva. Recommended treatment: topical corticosteroid therapy, a mast-cell inhibitor and cold compress.

### **Chemical conjunctivitis**

Results from irritant substances such as smoke, industrial pollution, sprays, alkalis and acids.

### **Viral conjunctivitis**

Caused by a wide range of viruses, commonly influenza virus, adenovirus and infectious mononucleosis, and by exanthems such as measles. Characterized by a watery discharge and redness of the conjunctiva. May be haemorrhagic. Usually self-limiting and no specific treatment is required unless caused by herpes simplex virus, in which case treatment with topical antiviral agents (aciclovir) as required.

### **Other causes of conjunctivitis**

Examples of causes are acute systemic disorders, i.e. Steven–Johnson syndrome and Kawasaki disease. Conjunctivitis is usually non-purulent and self-limiting, but in Steven–Johnson syndrome topical steroids are recommended. There are other systemic signs.

## **6.2 Other conjunctival disorders**

### **Subconjunctival haemorrhage**

May occur spontaneously or secondary to trauma, e.g. physical injury (such as non-accidental injury [NAI]), coughing (such as pertussis), seizure, post-birth or any activity involving Valsalva manoeuvres. Pertussis infection is an important cause. They usually resolve spontaneously within 2 weeks and do not require treatment.

### **Limbal dermoid**

May be isolated or part of syndrome, e.g. Goldenhar syndrome – coronal limbal dermoids appear as yellowish–white, usually rounded elevations, sometimes with pigmentation and hair at the apex.

### **Pigmented lesions**

Examples are pigmented limbal naevus, conjunctival haemangioma or increased vascularity, e.g. ataxia telangiectasia (usually on the temporal side of the bulbar conjunctiva), tumours and infiltrates of the conjunctiva, e.g. neurofibromatosis, sarcoidosis.

## 7. DISEASES OF THE CORNEA

### Developmental anomalies

- Total congenital corneal opacification is rare and needs urgent referral
- Microcornea corneal diameter is 9 mm or less, and may be associated with glaucoma, cataract, iris abnormalities or anterior segment dysgenesis
- Corneal dermoid cyst (limbal dermoid)
- Congenital coloboma

The cornea is also the site of many systemic diseases:

- Mucopolysaccharidosis (e.g. Hurler, Maroteaux–Lamy, Hurler–Scheie diseases) produces clouding of the cornea
- **Cystinosis** seen in the early months of life (involves the deposition of L-cystine in the cornea)
- **Glaucoma** produces hazy and opaque cornea due to corneal oedema
- **Wilson disease** produces Kayser–Fleischer ring (it is a greenish/grey ring along the outer margin of the cornea)
- **Infections** may cause corneal opacity, e.g. keratitis (also may be caused by vitamin A deficiency [rare] and injury)
- **Juvenile chronic arthritis** can cause band-shaped keratopathy (a cloudiness across the cornea, only in the interpalpebral fissure)
- **Keratoconus** characterized by thinning and bulging of the central cornea, which becomes cone shaped. Descemet membrane may occasionally rupture with sudden and marked corneal oedema (acute hydrops). Some degree of corneal scarring occurs. Mostly managed conservatively with contact lenses. Occasionally corneal transplantation is indicated. Usually sporadic. Associations with atopy, Down syndrome, Marfan syndrome, Ehlers–Danlos syndrome, aniridia and congenital rubella
- **Corneal inflammations** are associated with viral, bacterial, fungal and allergic diseases. Bacterial infection may cause corneal ulcers and abscesses, leading to visual impairment and corneal perforation. Herpes simplex infection of the cornea may be transmitted from the maternal birth canal or by direct contact with active lesion, and is a serious infection. Requires urgent attention and treatment with aciclovir

### Deposits

Corneal deposits are not easily visible. Slit-lamp examination is essential. Seen in cystinosis, uric acid crystals (brownish colour), calcium deposits and other rare conditions.

## 8. DISEASES OF THE SCLERA

Blue sclera, although seen in certain normal people. It is more common in osteogenesis imperfecta and Ehlers–Danlos syndrome.

Yellow discoloration of the sclera indicates jaundice. Black patches on the sclera may be due to either naevi or thinning of the sclera, which allows the colour of the choroid to show through.

Episcleritis is very rare in infants and children. Inflammation can be either nodular, as in the chickenpox lesion, or diffuse. Episcleritis is associated with subconjunctival injection and may involve the overlying conjunctiva as well. Usually causes mild ache in the eye.

Scleritis is characterized by pain on movement, deep redness and mild proptosis. The vision may be reduced by serous retinal detachment; association with Wegener granulomatosis.

**Episcleritis** and **scleritis** may occur in autoimmune disease, dry eyes and graft-versus-host disease.

## 9. PHOTOPHOBIA

**Definition:** light sensitivity in normal lighting conditions which makes the child uncomfortable.

### Causes of photophobia

**Systemic causes:** meningitis, encephalitis, migraine, vitamin A deficiency and xeroderma pigmentosum

**Drugs:** atropine eye drops, ethosuximide and *p*-aminosalicylic acid (PAS)

### Ophthalmic causes:

**Corneal:** most causes of true photophobia are of corneal origin, e.g. epithelial disruption, as with a foreign body. The most important cause of corneal photophobia is buphthalmos, which is the hallmark of congenital glaucoma. The corneas are enlarged due to breaks in Descemet membrane which allows stretching of the cornea in the infantile eye

**Iris:** aniridia, iritis

**Uvea:** photophobia may be present in albinism (absent uveal pigment) and uveitis. Juvenile chronic arthritis and spondyloarthropathy account for most cases of paediatric uveitis

Uveitis is classified according to location, clinical characteristics of the inflammatory pathology with further differentiation based on primary site such as iritis, choroiditis, iridocyclitis or panuveitis.

- **Anterior uveitis:** characterized by triad of symptoms: pain, redness and photophobia. Causes include trauma, conditions such as Kawasaki disease, Lyme disease, spondyloarthropathy and Crohn disease. In severe inflammation vision is reduced. Slit-lamp examination should be used to assess the extent of the inflammation and in diagnosis
- **Posterior uveitis:** inflammation of the choroid. The only symptoms are visual. Chorioretinitis

may be focal or diffuse, unilateral or bilateral. Causes include toxoplasmosis, cytomegalovirus (CMV) infection, sarcoidosis, syphilis, TB and toxocariasis. Signs are usually scarring and pigmentation often with visual impairment. Complications include retinal detachment and glaucoma

- **Lens diseases:** such as partial cataract.
- **Optic nerve disease:** optic neuritis (although the most important symptom is visual loss)
- **Vitritis**
- **Retinal problems:** retinal dystrophies especially cone dystrophies

## 10. CAUSES OF A PAINFUL RED EYE

- Trauma – haemorrhage
- Conjunctivitis (bacterial or viral)
- Uveitis
- Iridocyclitis
- Corneal damage: foreign bodies, direct injury, keratitis (e.g. herpes zoster and herpes simplex and other viral infections)
- Glaucoma
- Headache: eye pain but without red eye

These all need referral. A spontaneous subconjunctival haemorrhage in children is rare and although usually painless needs referral. Bacterial or allergic conjunctivitis usually does not need referral unless persistent or associated with lid swelling or periorbital oedema.

## 11. UVEAL TRACT DISORDERS (IRIS, CILIARY BODIES AND CHOROID)

### 11.1 Aniridia

Complete absence of the iris. Hereditary and sporadic forms. The usual mode of inheritance is an autosomal dominant trait. Aniridia occurs spontaneously in a third of such cases and they may have a chromosome 11p13 deletion.

#### Associations of aniridia

- Poor vision
- Cataract – 50–85% by the age of 20 years
- Glaucoma – not present at birth but later in childhood
- Optic nerve hypoplasia
- Ectopia lentis may also occur in conjunction with aniridia

#### Aniridia with systemic disease

WAGR syndrome: **W**ilms tumour, **a**niridia, **g**enitourinary abnormalities and **r**etardation. Deletion of the short arm of chromosome 11 usually present. High incidence of bilateral Wilms tumours.

## 11.2 Albinism

A hereditary error of metabolism within pigment cells. The loss of melanin may be limited to the eye (ocular albinism), or affect the skin and eye (oculocutaneous albinism).

### Ocular albinism

Usually inherited as X-linked.

#### Features

- Males with photophobia, reduced visual acuity, nystagmus and iris transillumination defects with foveal hypoplasia and scanty retinal pigmentation

### Oculocutaneous albinism

#### Tyrosinase negative

##### *Clinical picture*

Hair steely white, pink skin (sensitive to sunburn), reduced visual acuity, nystagmus – pink–blue eyes. This is associated with one or more of the lesions in the large tyrosinase gene at chromosome 11q14–21.

#### Tyrosinase positive

##### *Clinical picture*

Tyrosinase gene is normal. Usually has more pigment and therefore better vision.

### Albinism in conjunction with other diseases

- Chédiak–Higashi syndrome – autosomal recessive, albinism, repeated infections, mild bleeding diathesis, hepatosplenomegaly, peripheral and cranial neuropathy
- Hermansky–Pudlak syndrome – autosomal recessive, albinism, platelet dysfunction, pulmonary fibrosis and inflammatory bowel disease

## 11.3 Brushfield spots

These are silvery–grey spots on the iris. Found in 85% of children with Down syndrome and also in 24% of normal people.

## 11.4 Heterochromia iridis

Difference in iris colour. May be congenital or acquired.

### Congenital

- The involved iris is darker
- Horner syndrome: ipsilateral hypopigmentation, miosis and ptosis
- Waardenburg syndrome (autosomal dominant): lateral displacement of the inner canthi, prominent root of the nose, white forelock and sensorineural deafness

### Acquired

- Heterochromia may be result of infiltrative processes such as naevi and melanomatous tumours

## 11.5 Coloboma

Congenital defect due to failure of some portion of the eye or ocular adnexa to complete growth resulting in a cleft. They may occur as isolated defects or in association with systemic syndromes.

Usually sporadic, but isolated coloboma may be inherited as a dominant trait.

### Iris coloboma

Appears as a keyhole when complete and as a notch when partial; usually affects inferior and nasal part of the iris.

### Optic disc coloboma

Appears as a hole of variable size usually in the temporal side of the margin of the disc:

- CHARGE association: coloboma; heart disease; choanal atresia, retarded growth and development; genital hypoplasia; and ear anomalies
- Cat-eye syndrome: tri- or tetrasomy 22, colobomatous microphthalmia, anal atresia and preauricular skin tags
- 4P syndrome (Wolff–Hirschhorn syndrome): severe learning difficulties, characteristic face, fish-like mouth, coloboma, epicanthic fold, hypertelorism and squint, congenital heart disease
- Trisomy 13 (Patau syndrome): coloboma, cleft lip and palate, and severe cardiac abnormalities

### Iris abnormalities not related to coloboma

Nodular lesions of the iris may be seen in the neurofibromatosis (Lisch nodules).

## 11.6 Inflammation of the iris

### Iritis/iridocyclitis/uveitis

The incidence of iridocyclitis is approximately 20% in pauciarticular arthritis, more common in females with a ratio of 3:1. This is usually bilateral and asymptomatic and it may precede the arthritis. Common complications include band keratopathy, cataract and secondary glaucoma. As a result of the pain-free course of iridocyclitis associated with juvenile chronic arthritis, the recommended follow-up is required: 3-monthly for high risk (pauciarticular onset, ANA positive) and 6-monthly otherwise. Treatment includes topical corticosteroids and mydriatics.

Half of the patients with mild uveitis have an excellent prognosis, being controlled with topical medication.

**Other causes:** measles, mumps, chickenpox, Lyme disease, Kawasaki disease, Reiter syndrome, Behçet disease and sarcoidosis. Diagnosis is made through various immunological and serological tests.

## 12. ABNORMALITIES OF THE PUPIL

### Anisocoria

This is inequality of the pupils, and may be physiological or due to neurological disorders. In the absence of associated signs, diagnosis can be difficult as to which pupil is abnormal. Examination in light and dark will help to diagnose sympathetic and parasympathetic lesions. In Horner syndrome the anisocoria is greater in the dark, whereas in a parasympathetic lesion the difference is greatest in the light.

### Small pupil

- Horner syndrome
- Microcoria syndrome: congenital miosis – pupil <2 mm in size, when patient looks at a distant object
- Uveitis
- Drugs

### Large pupil

- Adie's (Tonic) pupil
- Nerve III lesion
- Trauma, aniridia, coloboma, complication of surgery and drugs (mydriatics, e.g. atropine)

### Abnormal shaped pupil

Coloboma (inferonasal), partial aniridia, hyperplastic pupillary membrane.



### **Tonic pupil syndrome (Adie syndrome)**

Children may present on school screening with failed vision or blurred near vision or photophobia. The effect is of a pupil slightly larger than the other pupil. Corneal sensation may be reduced. Patients may be hyporeflexic or areflexic with intact vibration sense.

### **Leukocoria**

White pupillary reflex.

### **Causes of leukocoria**

- Retinoblastoma
- Cataract
- Uveitis
- Retinopathy of prematurity
- *Toxocara* spp.
- Vitreous haemorrhage
- Coloboma

Diagnosis can often be made by direct examination of the eye with an ophthalmoscope. The absence of a red reflex requires immediate expert attention to determine the cause.

## **13. CHILDHOOD GLAUCOMA**

**Definition:** damage of the optic nerve with visual field loss caused by, or related to, elevated pressure within the eye. Normal intraocular pressure in infants and young children is <20 mmHg.

Congenital glaucoma begins within the first 3 years of life, juvenile glaucoma between the age of 3 and 30 years.

Classification broadly into:

- primary congenital glaucoma caused by an intrinsic disorder of the aqueous outflow mechanism
- secondary glaucoma caused by other ocular diseases or systemic abnormalities

When the intraocular pressure is raised in young children, the cornea usually becomes diffusely oedematous and enlarged. When the corneal diameter increases, splits occur in Descemet membrane and damage occurs to the corneal endothelial cells. If intraocular pressure is raised in a child under 2 years of age the eye may enlarge. This is referred to as ‘buphthalmos’ (ox-eye).

### **Clinical manifestations**

Symptoms include the classic triad of epiphora (tearing), photophobia and blepharospasm (eyelid squeezing) secondary to corneal irritation. However, only 30% of affected infants demonstrate the classic symptom complex. Epiphora in glaucoma is differentiated from nasolacrimal duct obstruction

by the presence of rhinorrhoea. When the nasolacrimal duct is obstructed, rhinorrhoea is absent. Other signs include corneal oedema, corneal and ocular enlargement, conjunctival injection and visual impairment.

## Primary congenital glaucoma

This is caused by an intrinsic disorder of the aqueous outflow drainage – more than 50% of glaucoma is primary; 1 in 10 000 births. Usually bilateral.

Associated ocular problems:

- Aniridia
- Sturge–Weber syndrome
- Neurofibromatosis
- Hypomelanosis of Ito
- Marfan syndrome
- Lowe syndrome
- Congenital rubella syndrome

## Secondary glaucoma

Associated conditions are inflammatory eye disease (in association with juvenile idiopathic arthritis [JIA]), ectopia lentis and complications of surgery for congenital cataract.

## Management of glaucoma

If untreated, glaucoma will inevitably lead to visual loss. Amblyopia is a major complication in unilateral glaucoma. The treatment remains surgical in most of the cases but sometimes medical treatment with drugs and laser therapy may help.

- **Surgical:** to establish more normal anterior chamber angle (goniotomy and trabeculectomy) or to reduce aqueous fluid production (cyclocryotherapy and photocyclocoagulation). Children may need several operations to lower the intraocular pressure. Long-term medical treatment may also be necessary
- **Medical:**  $\beta$  blockers (e.g. timolol) which act by lowering intraocular pressure. New medications such as betaxolol (Betopic) 0.25% have fewer systemic side effects
- **Cyclolaser therapy:** cyclophotocoagulation may be successful in reducing intraocular pressure. Repeated applications may be required because relapse is common

## 14. LENS DISORDERS

Characteristics to be considered are size, shape, location and transparency. The lens can be affected by developmental problems, humidity and systemic disease.

## 14.1 Developmental anomalies

The normal lens should fill the entire pupillary area. Aphakia (absent lens) and microphakia (small lens) are rare; the latter can be seen as part of microphthalmia in many of the congenital infections (TORCH).

## 14.2 Dislocated lens (ectopia lentis)

A subluxed lens is a lens partially displaced from its normal position but remaining within the pupillary space, whereas a dislocated or luxated lens is completely displaced from the pupil, implying separation of all or nearly all of the zonular attachments. A reduction in visual acuity is the most common presenting symptom of subluxation or dislocation of the lens.

### Presentation

Blurred vision.

### Associations

- Marfan syndrome: the most common cause of ectopia lentis (superiorly)
- Homocystinuria: the lens usually subluxes inferiorly; other causes include aniridia, trauma, coloboma and glaucoma
- Hereditary lens dislocation: usually bilateral

### Treatment

Visual improvement may be achieved with spectacles. A partially dislocated lens is often complicated by cataract formation, in which case the cataract has to be removed but should be delayed because of the possible complication of retinal detachment. Anterior dislocation of the lens may be treated with pupillary dilatation and manual repositioning of the lens by pressure on the cornea. Complete dislocation of the lens may lead to the development of glaucoma. Asymptomatic dislocation carries a very good prognosis.

## 14.3 Cataract

A cataract is a lens opacity. Its main presentation is visual impairment. Up to a third of children with bilateral congenital cataract remain legally blind even after surgery. Congenital cataract is the most common remedial cause of blindness in the developed world.

### Presentation

Absent red reflex, leukocoria, squint, nystagmus and visual impairment.

## Causes of a congenital cataract

- Idiopathic
- Intrauterine infection (TORCH)
- Genetic without systemic problems (autosomal dominant, recessive and X-linked inheritance)
- Genetic with systemic problems:
  - Autosomal dominant – hereditary spherocytosis, myotonic dystrophy, incontinentia pigmenti (rare), Marshall syndrome
  - Autosomal recessive (rare) – congenital ichthyosis, Conradi disease, Smith–Lemli–Opitz syndrome, Siemens' syndrome
  - X-linked inheritance (rare) – Lowe syndrome
- Chromosomal abnormalities (trisomy 21, 18 and 13) and Turner syndrome
- Metabolic disorders – galactosaemia, galactokinase deficiency and hypocalcaemia
- Maternal factors, e.g. diabetes mellitus, and drugs in pregnancy, e.g. corticosteroids and chlorpromazine

## Causes of acquired cataract

- Drugs such as corticosteroids
- Trauma
- Metabolic disorders (e.g. diabetes mellitus, hypothyroidism, hypocalcaemia and pseudohypoparathyroidism)
- Radiotherapy
- Infections – varicella, herpes simplex and *Toxocara canis*
- Atopic dermatitis
- Genetic conditions with later presentations such as Down syndrome, myotonic dystrophy, nail–patella syndrome, Alport syndrome, Wilson disease, Laurence–Moon–Biedl syndrome, Cockayne syndrome
- Cataract of prematurity
- The most common chromosomal abnormality associated with cataract is trisomy 21 usually later in life

**Bilateral congenital cataracts:** should be removed early because of interference with visual development.

**Partial cataracts:** need careful assessment of the density and size of the lens opacity before removal, because conservative management is indicated at least until the child's visual status can be adequately assessed. It is important that metabolic diseases such as galactosaemia, diabetes, hyperthyroidism and hypocalcaemia are ruled out through appropriate investigation. The most common operation for cataract is lensectomy and anterior vitrectomy in infants. Aphakic spectacles are required after surgery. In older children simple lens aspiration with or without implantation of the lens is the preferred procedure.

## 15. RETINAL DISORDERS

**Colobomas:** defects of closure of the embryonic fissure of the optic cup. It may occur unilaterally or bilaterally.

**Myelinated nerve fibres:** myelination may continue beyond the optic disc to include the retinal nerve-fibre layer. It is usually visible as yellow–white, flame-shaped patches oriented with the retinal nerve fibres. They may produce clinical signs of leukocoria.

**Albinism:** albino fundus, usually pale with poor macular development and prominent choroidal vasculature.

**Coat disease:** occurs in boys, peak at age 8–10 years, is predominantly unilateral. Peripheral retinal telangiectasias and aneurysmal dilatation lead to extensive areas of exudates giving the retina a yellow–white appearance, which may produce leukocoria.

**Retinitis pigmentosa (RP):** a pigmentary retinopathy characterized by night blindness (earliest symptom), progressive loss of peripheral visual field and loss of central vision (final symptom). Symptoms may be present in childhood, but usually do not become apparent until the second or third decade of life.

Early retinal changes shows pigment deposition as seen in the midperipheral retina, progressing to more diffuse pigment.

Systemic associations include:

- Abetalipoproteinaemia
- Refsum disease
- Usher syndrome
- Laurence–Moon–Biedl syndrome
- Kearns–Sayre syndrome

### Retinal detachment

This is a rare condition in childhood. Presentation is usually late and the disease advanced at the time of diagnosis. It often occurs in a developmentally abnormal eye and it may follow blunt trauma. Treatment is surgical.

### Hypertensive retinopathy

This is rare in children. In the early stages of hypertension no retinal changes are observed. Then the arterioles narrow and become irregular; retinal oedema will follow with the appearance of flame-shaped haemorrhages, cotton-wool spots (retinal nerve-fibre layer infarct) and papilloedema.

### Diabetic retinopathy

This is uncommon in children but may occur during or after puberty. Prevalence is related to duration and control of the disease.

Non-proliferative diabetic retinopathy is characterized by retinal microaneurysms, venous dilatation, and retinal haemorrhages and exudate. Proliferative form is characterized by neovascularization and proliferation of fibrovascular tissue on the retina. Most serious form.

## **Sickle cell retinopathy**

**Proliferative changes:** arteriolar occlusions leading to arteriovenous anastomosis. Vitreous haemorrhages and retinal detachment.

**Non-proliferative changes:** deposits, sunburst lesions and salmon-patch haemorrhages.

## **Retinopathy of prematurity**

This is vasoproliferative retinopathy affecting mainly premature infants. The clinical manifestations range from mild, which is usually transient changes of the peripheral retina, to severe vasoproliferative changes with scarring, leading to retinal detachment and blindness.

### **Classification**

There are five stages based on the location, extent and severity of the disease. The extent of the involvement of retinopathy is described as clock hours of retinal circumference affected.

Babies who at birth are <1500 g or who are 31 weeks' gestation or less should be screened.

### **Timing of the first examination**

- Infants born at or earlier than 25 weeks' gestation
- Screening at 6–7 weeks postnatally, then fortnightly until 36 weeks' postmenstrual age
- Infants born between 26 and 32 weeks' gestational age with screening at 6–7 weeks postnatally, and at 36 weeks postmenstrual age (or within a week of this to be discharged from hospital)

### **Treatment**

In selective cases, cryotherapy or laser photocoagulation of the peripheral avascular retina has been shown to be effective in stage 3 disease and to reduce progression to blinding disease. Recent advances in retinal surgical technique have led to some limited success in treatment of retinal detachment. The use of anti-VEGF (vascular endothelial growth factor) agents injected intravitreally may have a role to play in the management of some cases but the long-term effects (if any) of such agents on the developing neonatal neural system are as yet unknown.

### **Prevention**

Retinopathy of prematurity largely depends on prevention of premature birth and its associated problems. Despite improvement of our understanding of the natural history and the associated risk factors, such as high oxygen exposure, prevention remains a major challenge.

## Retinal haemorrhages

In young infants, by far the most common cause of retinal haemorrhage is non-accidental injury. The haemorrhages may last for many months. Haemorrhage rarely happens accidentally in children or as a complication of blood disorders such as leukaemia. Proper documentation by an ophthalmologist is essential.

## Retinoblastoma

This is the most common intraocular malignancy of childhood. Incidence – 1:14 000 to 1:20 000 births. Caused by a mutation in a growth-suppressor gene. Both alleles have to be affected to develop the tumour. The most common age of diagnosis is between 1 and 1½ years with 90% before the age of 3 years.

**Presenting signs:** leukocoria 60% and squint 22%. Less than 25% of all cases have a family history of retinoblastoma.

### Treatment

Enucleation of the eye remains the most common therapy, and will result in a cure if the tumour has not metastasized. Where bilateral tumour is present, the eye with the most extensive tumour with no possibility of useful vision is enucleated and attempts are made to save the eye with less involvement. Focal irradiation is used for solitary tumours <15 mm in diameter; systemic chemotherapy is also available to offer shrinkage of intraocular tumours, and cryotherapy and laser for small tumours.

Long-term follow-up and genetic counselling are required for patients with retinoblastomas.

## 16. INFECTIONS AND THE RETINA

### Congenital infections

- **Toxoplasmosis:** caused by *Toxoplasma gondii*. Congenital toxoplasmosis. Eight per cent of severely affected neonates will have chorioretinitis. Ophthalmological complications include chorioretinitis, which appears as a white elevated mass with surrounding pigmentation on the retina. Infants may present later with leukocoria or squint; visual deterioration occurs and retinal detachment is a complication. Treatment is with pyrimethamine and sulfadiazine both for 1 year
- **Rubella:** typical ocular findings include microphthalmia, microcornea, anterior uveitis, cataract, corneal opacification and glaucoma. The retinopathy in rubella is diffuse but does not affect vision
- **Cytomegalovirus:** ocular manifestation includes microphthalmia, cataracts, keratitis, choroiditis and optic atrophy. Diagnosis confirmed with tests and isolation of the virus from urine, stool or throat of the infected neonate. CMV retinitis is especially important to exclude and screen for in children after bone marrow transplantation or other organ transplantation if a CMV viral load is detected in the bloodstream
- **Herpes simplex:** the eye can be the site of disseminated herpes and the most common ocular

involvements are blepharoconjunctivitis with vesicles on the eyelids and keratitis. Choroiditis and inflammation of the vitreous with optic atrophy may also occur, particularly in infants with central nervous system involvement

- **HIV:** ocular manifestations include retinopathy, usually asymptomatic and characterized by cotton-wool spots, retinal haemorrhage and other microvascular abnormalities.
- **Syphilis:** causes bilateral chorioretinitis or salt-and-pepper fundus appearance

## Acquired infections

- **Toxocariasis:** ocular involvement rare. Caused by *Toxocara canis* larvae infection. The change is usually unilateral. Ocular forms include:
  - Endophthalmitis: present between the age of 2 and 9 years and most often confused with retinoblastoma because the red reflex is absent and a complete retinal detachment is present
  - Macular lesions: presents slightly later and usually a solitary granuloma

Presentation usually composed of strabismus and leukocoria or failed screening examination at school. Confirmation of infection with ELISA (enzyme-linked immunosorbent assay) for *Toxocara* spp. with peripheral eosinophilia on blood film.

**Treatment:** steroids and to a lesser extent anthelmintic drugs which are not very helpful and do not restore the lost vision.

## Bacterial endocarditis

May give picture of cotton-wool spots; frequently developed in patients with bacterial endocarditis as a result of septic emboli.

# 17. OPTIC NERVE DISORDERS

## 17.1 Papilloedema

Defined as swelling of the optic nerve in association with raised intracranial pressure. The vision is usually preserved even with marked swelling of the optic disc. The fundoscopic picture is as follows:

- Earliest sign is blurring of the disc margins, followed by elevated disc
- Dilated capillary plexus and retinal veins
- Absent pulsation of the optic disc
- Swollen nerve-fibre bundles
- Splinter haemorrhages and more markedly elevated disc; nerve-fibre infarcts (cotton-wool spots) and exudates follow
- Further engorgement and tortuosity of the retinal and disc capillaries, and haemorrhages become more widespread



## Causes of swollen disc in childhood

### Bilateral

- Papilloedema (raised intracranial pressure, hydrocephalus and benign intracranial hypertension)
- Hypertension
- Optic neuritis
- Bilateral pseudopapilloedema, as in myopia and hypermetropia
- Bilateral tumours (e.g. haemangioma, retinoblastoma and hamartoma)

### Unilateral

- Pseudopapilloedema as in myopia and myelinated nerve fibres and hypermetropia
- Tumours: haemangioma, retinoblastoma, optic nerve glioma
- Uveitis
- Ischaemic optic neuropathy
- Unilateral optic neuritis

## 17.2 Optic atrophy

The optic disc loses its colour and appears sharply demarcated with pale yellow–white disc. Usually leads to reduced visual acuity with subsequent visual field defects.

### Presentation

Bilateral optic atrophy presents as blindness in early infancy with roving eye movements and sluggish pupil reaction. Milder degrees of bilateral optic atrophy may cause minor visual defects or squint in childhood. Unilateral cases may present as a squint.

### Inheritance

Recessive or dominant trait.

Association with generalized neurological conditions such as Behr optic atrophy with cerebellar ataxia, hypotonia and learning difficulties.

Leber optic atrophy occurs in late adolescence, but secondary optic atrophy occurs to papilloedema, optic neuritis, compressive lesions of the optic nerve or chiasma, trauma and hereditary retinal disease or glaucoma.

## Causes of optic atrophy

- Prenatal:
  - maternal disease
  - pregnancy problems
- Perinatal:
  - prematurity
  - asphyxia
- Familial
- Ocular:
  - glaucoma
  - retinal dystrophy
- Compressive:
  - proptosis
  - space-occupying lesion
- Trauma
- Optic neuritis
- Toxic:
  - drugs
  - lead
- Meningitis/encephalitis
- Leukodystrophies

## 18. METABOLIC DISEASES AND THE EYE

### Corneal abnormality

- Mucopolysaccharidoses (except Hunter disease)
- Mucopolidosis
- Fabry disease
- Sialidosis
- Cystinosis
- Tyrosinaemia (type II)

### Visual failure

- Juvenile Batten disease
- Leukodystrophies
- Abetalipoproteinaemia
- Gangliosidoses

### Eye movement disorder

- Niemann–Pick disease type C, sialidosis type I (vertical gaze palsy)
- Gaucher disease type 3 (congenital oculomotor apraxia)

- Sialidosis type II (nystagmus), type I (nystagmus and myoclonus)
- GM2 gangliosidosis type III

## **Cherry-red spot**

- Tay–Sachs disease
- Sandhoff disease
- GM1 gangliosidosis type 1
- Niemann–Pick disease types A, C and D
- Sialidosis type 2
- Farber disease
- Mucopolipidosis I

## **19. MISCELLANEOUS DISORDERS**

### **Neurofibromatosis (NF1)**

- Plexiform neuromas of eyelids – often producing ptosis
- Conjunctival neurofibroma
- Lisch iris nodules
- Hamartomas (phakomas) of disc and retina
- Fundus pigmentary changes
- Optic gliomas
- Strabismus
- Nystagmus
- Proptosis and exophthalmos

### **Sturge–Weber syndrome**

- Glaucoma: 50% before the age of 2 years (20% after the age of 4)
- Choroidal haemangiomas – 40%

### **Wilson disease**

Kayser–Fleischer ring.

### **Tuberous sclerosis**

- Occurs in 50% of patients, although may not be evident in infancy
- Hamartomas of the retina and optic nerve – most common
- Papilloedema – rare
- Optic atrophy

## **The von Hippel–Lindau syndrome**

Retinal angiomatosis – usually in the midperiphery. Often multiple with both eyes involved in more than 50% of cases.

## **Ataxia–telangiectasia**

Telangiectasia of bulbar conjunctivae (by the age of 4–6 years), disorder of conjugate eye movements, convergent squint and nystagmus.

## **Incontinentia pigmenti**

Microphthalmos, corneal opacities, cataract and optic atrophy.

## **Marfan syndrome**

Lens dislocation (usually upward), and iridodonesis (tremulous iris), microphakia, cataract, myopia, glaucoma and retinal detachment.

## **Down syndrome**

Brushfield spots, cataract, chronic keratopathy, ectropion, glaucoma, keratoconus, lid eversion, myopia and strabismus.

## **20. OCULAR TRAUMA**

In order to assess the extent of ocular trauma vision should always be assessed first. The severity of the injuries is dictated by the amount of disruption to the anatomy. This varies from minor laceration of the eyelids to severe ocular injuries. Examination will require topical anaesthetic to examine the eye comfortably.

Blunt trauma to the eye may cause iritis or anterior uveitis. Patients will complain of dull eye pain and light sensitivity. Other signs of iritis include miosis of the pupil, excessive tearing and ciliary injection. A hyphaema is blood in the anterior chamber of the eye. Complications include re-bleeding, glaucoma and iron staining of the cornea. Dislocation of the lens may take place after blunt trauma.

Retinal haemorrhage may occur as a result of trauma.

Penetrating injuries to the eye may necessitate examination and should be brief and gentle in order to avoid exposure of the intraocular contents. Further examination is required in the operating room under anaesthesia. Topical medication should not be used in penetrating injuries.

## 21. ACQUIRED VISUAL LOSS

History is vital to ensure that visual loss is really acquired rather than present from birth:

- Cortical blindness
- Post-traumatic anoxia
- Hypotension
- Hypoglycaemia
- Migraine
- Occipital epilepsy
- Vitreous haemorrhage
- Retinal disease
- Optic nerve disease
- Optic neuritis
- Ischaemia
- Trauma
- Drugs
- Benign intracranial hypertension and pituitary tumour
- Hysteria

## 22. VISUAL ASSESSMENT AND REFRACTIVE ERRORS

### 22.1 Visual assessment

Visual acuity measurement is the most important test for assessment of visual function. The age of the child and the level of development dictate what type of test should be used. Fixation reflex is generally used to evaluate vision in young infants. A 3-month-old infant may be expected to steadily fixate and begin to follow pen light, toy or face, and by the age of 6 months a child should be able to follow a fixation target to all fields of gaze, so the level of vision can be estimated by the quality of fixation response.

From the age of  $2\frac{1}{2}$ –3 years objective measurement of visual acuity is possible.

### Testing the preverbal child

- Forced card preferential looking (FCPL): best for children up to 2 years old. Child is given a plain grey card to look at and on one end is a grating pattern. Attention is drawn to that end if child sees the grating acuity pattern at a third of a metre
- Cardiff Acuity Cards: best for children between 2 and 4 years of age – child's gaze is directed to shapes on grey cards held 50–100 cm from the child

### Testing verbal children

- Kay pictures: child names different shapes at 3 metres either with or without a matching card
- LogMAR or Snellen chart with or without matching card

## 22.2 Refractive errors

Errors in the refractive power of the eye may lead to subnormal visual acuity. This may result from variation of curvature of the cornea or lens or variation in the axial length of the eye.

The following are the most common forms of refractive error:

- **Myopia** (short-sightedness): this is usually due to an increase in axial length of the eye so objects at distance are blurred. Myopia is inherited as a multifactorial trait, which may also be associated with systemic conditions such as Stickler syndrome. Concave lenses are used to correct myopia in most circumstances
- **Hypermetropia** (far-sightedness): the optical image formed by the hypermetropic eye is focused behind the retina because the visual axis is short, and therefore convex lenses are used
- **Astigmatism**: this occurs when the cornea, lens or retinal surface has a toric rather than a spherical shape. This produces a blurred retinal image of object at any distance. Astigmatism can be corrected by special lenses
- **Anisometropia**: this refers to a condition where the eyes have different refractive errors, with one worse than the other. It may occur with myopia, astigmatism or absence of the lens, or a combination of these refractive errors

## 23. OPHTHALMOLOGICAL INVESTIGATIONS

### Visual evoked potentials

This test is used to define vision development in infants. This measures the time taken for a light stimulus to pass along the visual pathway to the occipital cortex and also the amplitude of the response.

### Electroretinography

Electroretinography (ERG) is an electrical recording of the response of the retina to visual stimulus, e.g. flash of light. This test is useful in the detection of retinitis pigmentosa and intraocular foreign bodies.

### Electro-oculography

This is based on the standing potential of the eye. The electro-oculogram (EOG) is recorded by placing skin electrodes adjacent to the inner and outer canthi of the eye. It is useful in detecting hereditary macular disease and also retinitis pigmentosa and myopic chorioretinal degeneration, and

helps in diagnosis of Best disease.

## **Ultrasonography**

This can be used at times to detect ocular abnormalities that are not usually clinically visualized, such as opacification of the cornea, lens and vitreous.

## **Slit-lamp examination (biomicroscopy)**

This is used to view various structures of the eye and optical section, e.g., cornea, aqueous, humour, lens and vitreous, by providing a magnified view. It is often crucial in trauma and in cases such as iritis.

## **Colour vision**

This is usually performed by using standard Ishihara colour plates with some adaptation of the usual testing techniques. Ishihara plates test only red/green colour vision deficiency. Other plates may be used to include blue/yellow testing.

The test is accomplished whenever a child is able to name or trace the test symbol.

Colour vision defect is inherited as an X-linked pattern of inheritance but can also be acquired secondary to optic or macular disease, as in retinitis pigmentosa, and also as a side effect of drugs such as rifampicin.

## **Visual field assessment**

This depends on the age and ability of the child. In infants this can be performed by simple confrontation techniques. The infant sits on a carer's lap and the examiner faces the child and attracts his or her attention centrally, using a toy or a light moved silently from the periphery. A child with normal fields will readily move his or her head or eyes in the direction of the object or light source.

More formal visual tests can be performed in older children using Goldmann visual field testing.

## **Ocular coherence tomography**

Ocular coherence tomography (OCT) allows visualization of the different layers of the retina and is extremely useful to detect anatomical abnormalities.

## **Autofluorescence**

Autofluorescence (AF) detects lipofucins fluorescence. It is used to detect retinal dystrophies and can also detect drusen at the optic nerve head.

## 24. THE VISUALLY IMPAIRED CHILD

### Assessing the visually impaired child

A child may be visually impaired and be:

- systemically and developmentally normal: examine the eyes and also look for nystagmus (may be a sign of foveal hypoplasia)
- systemically unwell: metabolic disease or neurometabolic disease
- developmentally delayed: consider cortical visual impairment, especially in premature infants

### Helping the visually impaired child

Every visually impaired child should be registered as severely visually impaired (with best corrected visual acuity):

- Visual acuity of  $<3/60$  with a full visual field
- Visual acuity between  $3/60$  and  $6/60$  with a severe reduction of field of vision, such as tunnel vision
- Visual acuity of  $6/60$  or above but with a very reduced field of vision, especially if a lot of sight is missing in the lower part of the field

or partially visually impaired (with best corrected visual acuity):

- Visual acuity of  $3/60$  to  $6/60$  with a full field of vision
- Visual acuity of up to  $6/24$  with a moderate reduction of field of vision or with a central part of vision that is cloudy or blurry
- Visual acuity of up to  $6/18$  if a large part of field of vision, e.g. a whole half of vision, is missing or a lot of peripheral vision is missing

Children should be referred to a teacher for the visually impaired and should have a statement of educational needs.

## 25. FURTHER READING

American Academy of Ophthalmology (2011–2012). *Basic and Clinical Science Course*, Vol 1 Update on *General Medicine*; Vol 6 *Pediatric Ophthalmology and Strabismus*. San Francisco, CA: American Academy of Ophthalmology.

Athreya B (1980). *Clinical Methods in Pediatric Diagnosis*. London: Van Nostrand Reinhold.

Behrman R, Kleigman R, Jenson H (2000). *Nelson Textbook of Paediatrics*, 16th edn. Philadelphia, PA: WB Saunders.



- Brodsky M (2010). *Pediatric Neuro-Ophthalmology*. New York: Springer Verlag.
- Polnay L, Hull D (1985). *Community Paediatrics*. Edinburgh: Churchill Livingstone.
- Taylor D, Hoyt C, eds (2005). *Pediatric Ophthalmology and Strabismus*, 3rd edn. Philadelphia, PA: Elsevier Saunders Ltd.
- Vaughan D, Taylor A (1986). *General Ophthalmology*, 11th edn. London: Lange.
- Wright KW, Spiegel P (2002). *Pediatric Ophthalmology and Strabismus*. New York: Springer Verlag.
- Zitelli B, Dans H, eds (1992). *Paediatric Ophthalmology*, 2nd edn. New York: Gower Medical Publishing.

## **CONTENTS**

### **1. Introduction**

### **2. Embryology**

### **3. Trauma**

[3.1 Anatomical and physiological differences in the paediatric skeleton](#)

[3.2 Injuries unique to the immature skeleton](#)

[3.3 Injuries involving the upper limb](#)

[3.4 Injuries involving the lower limb](#)

### **4. Metabolic disorders**

[4.1 Rickets and osteomalacia](#)

[4.2 Osteogenesis imperfecta](#)

[4.3 Idiopathic juvenile osteoporosis](#)

### **5. Neuromuscular disorders**

[5.1 Arthrogrypotic syndromes](#)

[5.2 Spina bifida \(myelomeningocele\)](#)

[5.3 Myopathies](#)

### **6. Lower limb**

[6.1 Developmental dysplasia of the hip](#)

[6.2 Perthes disease \(Legg–Calvé–Perthes disease\)](#)

[6.3 Slipped capital femoral epiphysis](#)

[6.4 Congenital talipes equinovarus](#)

[6.5 Irritable hip](#)

[6.6 Management of a limping child](#)

## **[7. Upper limb](#)**

[7.1 Orthopaedic brachial plexus palsy](#)

[7.2 Trigger thumb](#)

## **[8. Infection](#)**

[8.1 Osteomyelitis](#)

[8.2 Septic arthritis](#)

## **[9. Paediatric spine](#)**

[9.1 Scoliosis](#)

[9.2 Kyphosis](#)

## **[10. Further reading](#)**

---

# Orthopaedics

---

## 1. INTRODUCTION

This chapter aims to provide the doctor who is training to be a paediatrician with an insight into the subspecialty of paediatric orthopaedics. The contents of this chapter are by no means exhaustive but will offer a mode of quick revision to the paediatrician.

## 2. EMBRYOLOGY

- The primitive streak appears at about 12 days after conception
- Caudally, cells migrate from ectoderm and endoderm to form mesoderm. The mesoderm forms the connective tissue
- Cranially, the formation of the notochord appears in the second to third week of gestation
- Neural crest cells differentiate to form the peripheral and autonomic nervous systems
- Somites form on each other side of the notochord and develop into a specific dermatome, myotome and sclerotome
- Limb buds develop between 4 and 6 weeks
- Bone develops either in a cartilage model (endochondral ossification) or in a membrane model (intramembranous ossification)
- Primary ossification centres appear between 7 and 12 weeks. They form in the midportion of the bone anlage. This is responsible for the formation of the diaphysis and the metaphysis
- Secondary ossification centres develop in the chondroepiphysis. The ossification centre for the distal femur occurs at 40 weeks' gestation. This is of medicolegal importance because the presence of this centre is indicative of a complete pregnancy. All the other secondary centres occur postnatally
- There are two types of growth plates
  - Physis – which responds to compressive forces
  - Apophysis – which responds to tensile forces

## 3. TRAUMA

- Orthopaedic trauma accounts for 15–20% of accident and emergency department visits in the UK

- There are a number of anatomical and physiological variations in the paediatric skeleton that make this practice different from that of adult practice

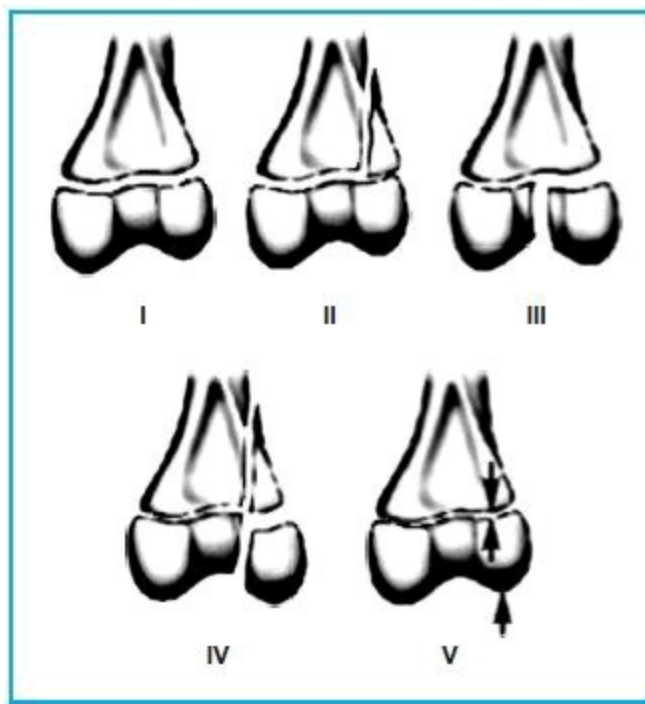
### 3.1 Anatomical and physiological differences in the paediatric skeleton

- The bony architecture in children includes a thick periosteum, a growth plate (physis) and an epiphysis (secondary ossification centre)
- The immature skeleton is much more elastic and hence absorbs more stress before actually breaking
- The ligaments are stronger than the epiphyseal plates to which they are attached, so the incidence of sprains and ligamentous injuries is far less in children than of avulsion fractures of the ends of the bones
- The periosteum is thick and extremely active, producing abundant callus aiding fracture healing. Non-unions are rare in paediatrics
- Remodelling helps with reshaping of a healed fracture
- The younger the patient and the closer the fracture is to a joint (metaphysis of long bones), the greater the potential to remodel
- Deformities occurring in the plane of motion of the adjacent joint will also remodel better than otherwise, i.e. a dorsovolar deformity in the distal end of the radius will remodel better than a fracture that has healed with radial or ulnar deviation

### 3.2 Injuries unique to the immature skeleton

#### **Growth plate (physeal) fractures**

- Up to 30% of paediatric fractures involve the growth plate. Most such fractures occur through the hypertrophic zone. The commonest site of growth plate fractures is the distal radius and ulna
- A widely used and accepted classification system was designed by Salter and Harris. This classification system also has significant prognostic and treatment implications



The Salter–Harris classification of growth plate injuries

## Greenstick fractures

- Greenstick fractures are the most common (50%) fracture affecting children. They are also called **unicortical fractures** because one cortex is in continuity. The fracture may be rotated and angulated

## Buckle fractures and plastic deformation

- After axial loading, buckling of the metaphyseal bone occurs, leading to a buckle or torus fracture. This is a very stable fracture and often all that is needed is a few weeks of immobilization for pain relief
- Paediatric bone is more elastic than adult bone – it absorbs more energy before fracturing. This leads to more deformation of the bone before breaking and hence there is a recognized entity called plastic deformation which is quite regularly seen in a child after an injury
- There is no breach of the cortex but a deformity of the bone is seen

## 3.3 Injuries involving the upper limb

### Shoulder

- The clavicle is the most commonly fractured long bone in a child
- Most of these fractures heal well with non-surgical management methods
- Note that the clavicle has two primary ossifying centres. This can be confused with a fracture

### Proximal humeral fractures

- Usually heal well with non-surgical management, with good potential for remodelling
- Humeral shaft fractures should be evaluated with a good history and clinical examination. These fractures are not common without significant violence. If there is no appropriate history, there should be a high index of suspicion about non-accidental injury, especially if the fracture is spiral

## **Elbow**

- The most common fractures in the elbow occur in the distal humerus. About 75% of such fractures affect the supracondylar region
- Supracondylar fractures occur through the distal metaphysis of the humerus
- Clinical examination is very important to assess the vascularity and nerve supply distal to the fracture. Compartment syndrome should be considered. Any of the three major nerves can be affected by this fracture
- A vascular insult can cause the Volkman ischaemic contracture (about 1–2%). Ischaemia causes fibrotic contractures in the forearm muscles. Treatment depends on the type of fracture, varying from just immobilization of the affected elbow to manipulation under anaesthesia and stabilization with wires

## **Forearm, wrist and hand**

- A Monteggia fracture is a complex injury where there is an ulnar shaft fracture and dislocation of the radial head
- A Galeazzi fracture is the association of a fracture of the shaft of the radius and disruption of the inferior radioulnar joint
- Treatment options range from manipulation under anaesthesia to open reduction and internal fixation
- Distal radial fractures are common, especially when the child falls on to the outstretched hand. Salter–Harris type 2 fractures are the most common fractures affecting the distal radius
- Boxer fractures (neck of the fifth metacarpal) are common in the late teens when they suffer a punching injury

## **3.4 Injuries involving the lower limb**

### **Pelvis and hip**

- Uncommon
- Usually caused by high-velocity road traffic accidents
- Treatment depends on the classification and displacement. It may include:
  - Manipulation under anaesthesia
  - Hip spica
  - Closed or open reduction with internal fixation
- Complications include:
  - Avascular necrosis (incidence of approximately 40%)

- Growth arrest leading to deformities such as coxa vara
- Non-union which has an incidence of about 5%

## **Femur fractures**

- Incidence is about 1% in children aged <12 years
- Peak age is between 2 and 5 years
- 70% occur in the middle third, 20% in the proximal third and 10% in the distal third
- The Waddell triad – fractured femur, head injury and thoracic injury
- Consider non-accidental injury in a child with a femur fracture
- Clinical symptoms include pain and deformity. Examine for distal neurovascular deficit
- Treatment – analgesia, splinting, traction, spica, internal fixation (plate osteosynthesis, intramedullary nails)
- Complications include leg-length discrepancies

## **Fractures of the tibia and fibula**

- Most common lower limb fractures in children
- Account for about a fifth of paediatric long bone fractures
- Clinical symptoms – pain and deformity. Assess neurovascular status
- Fracture in toddlers – spiral fracture of the tibia in a child between 9 months and 3 years:
  - Low-energy injury
  - Leads to a limp and to localized warmth and tenderness
  - Child usually crawls and prefers not to weight bear
  - Radiographs may be inconclusive initially
  - Usually heal with no trouble
- Treatment generally includes analgesia, splinting. Surgical treatment involves plating, nailing or external fixation

## **Knee**

The main injuries include meniscal injuries, anterior cruciate ligament injuries and osteochondral defects. Others include Osgood–Schlatter disease and chondromalacia patellae.

- **Meniscal injuries:**
  - Usually a twisting injury
  - Symptoms include pain, effusion, locking, giving way and snapping
  - Evaluation consists of clinical examination, diagnostic arthroscopy and magnetic resonance imaging (MRI)
  - Treatment is arthroscopic, performing either a meniscal repair or partial menisectomy
- **Discoid meniscus**
  - Congenital abnormality caused by the failure of absorption of the central portion of the meniscus
  - Incidence is between 3 and 15%, the lateral meniscus being more commonly affected
  - Symptoms include lateral knee pain, locking or loud clunking. Children sometimes find it unable



to fully extend the knee

- Treatment: if symptomatic then needs an arthroscopic partial menisectomy

- **Anterior cruciate ligament (ACL) injury:**

- Incidence 0.3/1000 per year
- Usually a sporting injury
- Can be associated with injury to other ligaments
- Management involves physiotherapy
- Surgical treatment involves either fixing the avulsed bony fragment or carrying out an ACL reconstruction

- **Osteochondral defects (osteochondritis dissecans):**

- Defect involving bone and cartilage within the knee
- Causes discontinuity of the articular cartilage
- Aetiology unknown
- Most commonly seen in the lateral part of the medial femoral condyle
- Signs and symptoms – pain, locking, effusion, may present with an acutely locked knee
- Treatment – analgesia, rest, splintage (if subchondral bone is intact)
- Arthroscopic assessment is required. If there is a ‘loose body’ then that should be removed. Fixation of the fragment may be undertaken if it’s amenable

- **Osgood–Schlatter disease:**

- Inflammation of the tibial tubercle as a result of repeated tensile forces
- Incidence of about 2% of all growth plate injuries
- Generally a self-limiting condition; bilateral in about a third of patients; boys affected more than girls
- Rest and analgesia are all that may be required

- **Adolescent anterior knee pain:**

- Pain about the knee is a common complaint. Initially hip pathology should be excluded
- Usually synonymous with chondromalacia patellae (softening of the retropatellar cartilage)
- Patellofemoral maltracking is usually the cause
- Other causes such as trauma, infection and neoplasm must be excluded
- Treatment is usually physiotherapy but surgery may be required in some selected cases

## **Foot and ankle**

- **Ankle fractures** are classified using the Salter–Harris classification:

- Usually caused by a twisting force
- Cause pain, deformity, swelling
- Radiographs are usually conclusive
- Treatment includes splintage and analgesia. Can be treated by open reduction and internal fixation

- **Tarsal and metatarsal fractures** occur frequently in the adolescent patient. Diagnosis can prove difficult:

- Treatment is usually by splintage and analgesia. Internal fixation is rarely required

## **4. METABOLIC DISORDERS**

Bone metabolism is explained in detail in Chapter 9.

## 4.1 Rickets and osteomalacia

- Occurs when there is a decrease in serum calcium (may be just the ionized component) or phosphorus or both
- Causes growth abnormalities and abnormal mineralization of the skeleton in children (**rickets**)
- Affects the mineralization of the skeleton in an adult (**osteomalacia**)

### Clinical manifestations

- Apathetic and irritable
- Short attention span
- Short stature (height below the third percentile)
- Frontal bossing
- Enlargement of skull sutures (hot-cross bun skull)
- Delayed dentition
- Enlargement of costal cartilages (rachitic rosary)
- Pectus carinatum
- Delayed weight-bearing milestones
- Deformities of lower limbs (genu varum)
- Enlarged epiphyseal regions of the long bones

### Radiological findings

- Cupping and widening of epiphysis
- Osteopenia of the metaphysis
- The Looser zones represent areas of weakening in the bone. Although they can predispose to fractures, they do not themselves imply that there is a fracture

### Further investigation

- Serum calcium, vitamin D and parathyroid hormone (PTH) levels

### Treatment

- Exposure to sunlight
- Vitamin D supplementation (dose depends on the vitamin D/PTH levels)

## 4.2 Osteogenesis imperfecta

- Defect in type 1 collagen

- Four types have been identified by Silience

## Types of osteogenesis imperfecta defined by Silience

Type	Inheritance	Sclerae	Features
I	AD	Blue	Hearing loss IA – teeth affected IB – teeth not affected
II	AR	Blue	Lethal
III	AR	Normal	Fractures at birth short stature
IV	AD	Normal	Milder, normal hearing

AD, autosomal dominant; AR, autosomal recessive.

## Clinical features

- Increased fragility of bones but fracture healing process is unaffected
- Short stature
- Scoliosis
- Defective dentinogenesis
- Conductive deafness
- Ligamentous laxity
- Blue sclerae and tympanic membranes

## Diagnosis

- History
- Clinical examination
- Radiographs – thin cortices and osteopenia
- Histologically – wide haversian canals, osteocyte lacunae

## Management

- Aims include fracture management and rehabilitation
- May need special techniques to aid fracture management (i.e. Sofield osteotomy)
- Ideally would have an internal fixation
- Calcitonin and calcium supplements reduce the incidence of fractures
- Bisphosphonates

## 4.3 Idiopathic juvenile osteoporosis

- Reduction in mineral and matrix (compare osteomalacia where there is normal matrix but reduced mineral)

- Rare
- Self-limiting
- Age of onset usually between 8 and 14 years
- Resolves spontaneously by 3–4 years after onset

## **Clinical features**

- Bone and joint pain
- Growth arrest
- Vertebral collapse
- Metaphyseal fractures
- Diaphysis is less affected (compare osteogenesis Imperfecta in which bone is uniformly affected)

## **Diagnosis**

- Serum calcium and phosphorus are normal
- Alkaline phosphatase is normal or slightly elevated
- Hypercalciuria may be present
- Diagnosis is usually by exclusion
- Differential diagnoses – osteogenesis imperfecta, haematological malignancies, thyrotoxicosis, Cushing syndrome

## **Management**

- Treatment of fractures is similar to that in the normal child
- Bracing for scoliosis

# **5. NEUROMUSCULAR DISORDERS**

## **5.1 Arthrogrypotic syndromes**

### **Arthrogryposis multiplex congenita**

- Non-progressive disorder
- Congenitally rigid joints
- Sensory function is maintained but there is loss of motor function (may mimic polio)

### **Aetiology**

- May be neuropathic, myopathic or mixed
- Decrease in anterior horn cells in the spinal cord

### **Possible associations**

- Oligohydramnios
- Intrauterine viral infection

## **Clinical features**

- Normal facies
- Normal intelligence
- Multiple joint contractures
- No visceral abnormalities
- Associated with teratological hip dislocations, club feet and vertical talus
- C-shaped scoliosis

## **Treatment**

- Orthopaedically it is aimed at release of soft-tissue contractures, physiotherapy and functional bracing

## **Distal arthrogryposis syndrome**

- Autosomal dominant disorder
- Predominantly affects the hands and feet
- Ulnar deviation of fingers, flexion contractures at the metacarpophalangeal and proximal interphalangeal joints
- Club foot and vertical talus

## **Larsen syndrome**

- Joints less rigid than in arthrogryposis
- Multiple joint dislocations
- Flattened facies
- Scoliosis
- Cervical kyphosis

## **5.2 Spina bifida (myelomeningocele)**

This is a disorder of incomplete spinal cord closure or rupture of the cord secondary to hydrocephalus. It can be:

- Spina bifida occulta (defects in the bony vertebral arch but intact cord structures)
- Meningocele (sac of meninges without the neural elements)
- Myelomeningocele (sac of meninges with the protruding neural elements)
- Rachischisis (exposed neural elements with no meninges)

## **Antenatal diagnosis**

- Raised  $\alpha$ -fetoprotein
- Ultrasound (anomaly visible on scan)

## Clinical features

- Neonatal findings such as hip dislocations, hyperextension of the knee, and club feet are common
- Fractures are common but, as there are problems with sensory function, diagnosis can be difficult
- Signs and symptoms depend on the level of the spinal defect
- Increased incidence of allergic reactions, mainly latex sensitivity
- **Hips:**
  - Flexion contractures with higher level involvement
  - Dislocation of the hip
  - Late hip dislocation can be a sign of tethering of the cord
- **Knees:**
  - Quadriceps weakness causing difficulty in ambulation (key level is L4)
  - Flexion contractures
  - Valgus deformity
- **Ankle and foot:**
  - Rigid club foot
  - Tight Achilles tendon
  - Valgus hind foot
- **Spine:**
  - Scoliosis can be bony or muscular (thoracic level paraplegia) in origin
  - Rapid curve progression can denote hydrocephalus or a tethered cord

## Principles of treatment

Treatment should be directed to mobilize the patient:

- Soft-tissue contracture release
- Corrective osteotomy, as required
- Functional bracing
- Surgical treatment may be required, directed at a specific problem, i.e. hip dislocation or scoliosis
- Specialized physiotherapy
- Custom-made wheelchair

## 5.3 Myopathies

### Duchenne muscular dystrophy

- This is a sex-linked recessive myopathy
- ‘Clumsy walking’
- Calf pseudohypertrophy

- Gower sign is positive (gets up using the hands to move up the body to compensate for loss of antigravity muscles)
- Hip extensors are the muscle groups to be affected first
- Markedly elevated creatine phosphokinase
- Muscle biopsy shows absent dystrophin
- Muscle biopsy also shows foci of necrotic tissue infiltration
- Treatment is directed to keeping the patient ambulatory
- Patients are usually wheelchair bound by age 15 years
- Scoliosis is a major concern in treatment

## **Becker muscular dystrophy**

- This is a sex-linked recessive myopathy
- Similar to Duchenne muscular dystrophy but less severe clinical picture
- Red/green colour blindness
- Patients live beyond their teens
- Dystrophin is present but abnormal

## **Facioscapulohumeral dystrophy**

- This is an autosomal dominant disorder
- Facial abnormalities
- Winging of scapula
- Normal creatine phosphokinase

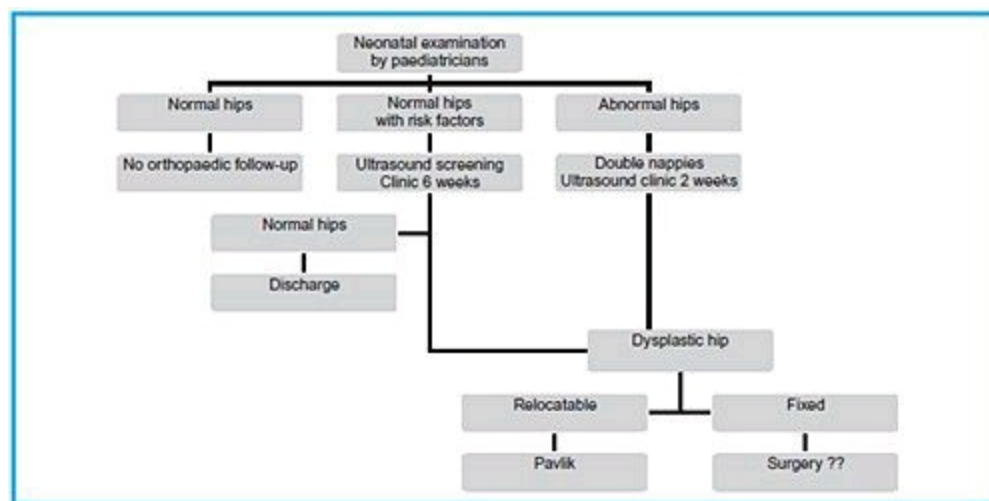
## **Myotonic myopathies**

- **Myotonia congenita:**
  - Defect is in chromosome 7
  - Affects chloride channels in the muscles
  - Hypertrophy seen with no weakness of muscles
  - Improves with exercise
- **Paramyotonia congenita:**
  - Defect is in chromosome 17
  - Affects the sodium channels in the muscles
  - Symptoms worsen with exposure to cold
  - Worse in distal upper extremity
- **Dystrophic myotonia:**
  - Defect is in chromosome 19
  - Small gonads
  - Low IQ
  - Distal involvement

## 6. LOWER LIMB

### 6.1 Developmental dysplasia of the hip

- Comprises a spectrum of abnormalities from complete dislocation of the hip to mild acetabular dysplasia
- Types of developmental hip dysplasia include dislocated hip, dislocatable hip, subluxable hip and dysplastic hip
- Incidence is 1 in 1000 for established dislocation (15 per 1000 for neonatal instability)
- Risk factors include being firstborn, being female, having a breech presentation and family history
- Other associated conditions include congenital torticollis, skull or facial abnormalities, hyperextension of the knee and club feet
- Clinical examination includes the Ortolani test (for reducing a dislocated hip) and the Barlow test (for dislocatable or subluxatable hip)
- Hip click suggests an audible or palpable noise while examining the hips, when there are no signs of instability
- Thigh skin creases may or may not be asymmetrical
- Teratological dislocation means that there are other associated conditions such as arthrogryposis. These are typically stiff, high-riding and irreducible dislocations
- Screening for this diagnosis includes a neonatal physical examination and, possibly, ultrasound of the hips
- Screening can be general (all newborn babies undergo an ultrasound examination) or selective (only babies with specific risk factors undergo ultrasound). A protocol is illustrated opposite



Protocol for management of developmental hip dysplasia

### Treatments

- Early diagnosis – Pavlik harness has a success rate of about 85%
- Failed Pavlik harness or late presenters (>3 months) will undergo either a closed or an open reduction augmented with a hip spica
- Late presenters, aged >2 years, will almost certainly have, along with the above procedure, a femoral shortening osteotomy



- Even with a successful closed reduction, about 50% of patients will need a pelvic osteotomy later because there is usually a residual acetabular dysplasia

## **Complications**

- Avascular necrosis of the proximal femoral physis
- Growth disturbances
- Coxa magna
- Residual acetabular dysplasia

## **6.2 Perthes disease (Legg–Calvé–Perthes disease)**

This is a non-inflammatory deformity of the femoral head caused by a vascular insult leading to osteo-necrosis of the capital femoral epiphysis:

- It affects more boys than girls (4:1)
- Usually presents between 4 and 8 years of age (can have a secondary peak between 10 and 12 years)
- Delayed skeletal maturation
- Increased incidence with a positive family history or low birthweight

## **Clinical features**

- Pain (may present with referred pain in the knee)
- Decreased range of motion
- Limp
- Skeletal age at onset is a significant indicator of prognosis (onset at more than 6 years carries a significantly poorer prognosis)
- 15% bilateral involvement (always asymmetrical involvement, compared with multiple epiphyseal dysplasia which is symmetrical)
- Differential diagnosis includes septic arthritis of the hip, epiphyseal dysplasia and hypothyroidism

## **Investigation**

- This is by plain radiograph of the pelvis with both hips anteroposterior and frog lateral views

## **Stages**

- Initial stage
- Fragmentation
- Healing
- Residual

# Severity

This is described in many ways but the most commonly used classification is the Herring lateral pillar classification:

- Group A – lateral pillar, lateral third of the femoral head shows collapse of less than 30%
- Group B – 30–50% collapse
- Group C – >50% collapse of the lateral third of the capital femoral epiphysis

# Treatment

- Aims to maintain the range of movement and to contain the femoral head in the acetabulum. Soft-tissue release and corrective osteotomy may be required to achieve this

## 6.3 Slipped capital femoral epiphysis

Displacement or slipping of the proximal femoral epiphysis on the neck (this is a misnomer and it is usually the neck that slips out of alignment with the head; the head stays in the acetabulum). The defect is in the hypertrophic zone of the growth plate.

# Incidence

- 2–10 in 100 000
- Commonly seen in adolescent boys
- Risk factors – obesity, positive family history
- Can be bilateral in about 25% of cases

# Clinical symptoms

- Pain in the hip or knee
- Antalgic gait
- Externally rotated limb
- Decreased internal rotation of the affected limb

# Classification

Classification depends on the duration of the symptoms or on ability:

- Acute – <3 weeks
- Acute on chronic
- Chronic – >3 weeks
- Stable (can weight bear) or unstable (unable to weight bear)

## Investigations

- Plain anteroposterior radiograph of the pelvis and frog lateral views
- Grading on the extent of slip

## Treatment

- Screw fixation of the epiphysis
- Corrective osteotomy may be required in delayed presentations
- Prophylactic pinning of the contralateral hip may be considered
- Complications include avascular necrosis of the femoral head and chondrolysis

## 6.4 Congenital talipes equinovarus

- Also called 'club foot'
- Incidence is 1 in 1000
- Male:female ratio is 2:1
- No known causes but definite genetic preponderance
- Various theories, such as fetal developmental arrest, myogenic and neurogenic problems, or retracting fibrosis, have been put forward
- Various associations, such as Streeter dysplasia, diastrophic dwarfism, arthrogryposis and myelomeningocele, have been documented
- Two types: positional (where the deformity is passively, fully correctable) and structural or rigid (where the deformity cannot be passively corrected)
- It is a three-dimensional deformity involving forefoot adduction and supination with hindfoot equinus and varus
- Earlier treatment improves prognosis
- Treatment can be either non-surgical (serial casting, splinting) or surgical (soft-tissue release with or without corrective osteotomy)

## 6.5 Irritable hip

- Is an idiopathic benign inflammation of the hip joint, which is one of the most common causes of admission to a paediatric orthopaedic unit
- May be confused with septic arthritis but severe spasm, tenderness, pyrexia and a raised CRP (C-reactive protein) differentiate sepsis
- Perthes disease can be identified on an initial radiograph. If in doubt a repeat radiograph is undertaken after an interval to compare
- Irritable hip usually resolves on its own after the first episode
- Management: reassurance, analgesics and physiotherapy (if required) to maintain the range of movement. Bed rest and traction may help if the pain is severe

## 6.6 Management of a limping child

- History is important, with special emphasis on duration, method of onset and predisposing illness (if any). Development history should also be obtained
- Types of limp:
  - Short-limbed gait, is caused by lower limb length discrepancy (toe walking could be adaptive manoeuvre, usually by the younger child)
  - Antalgic gait, caused by pain. Patients prefer to spend less time on the painful limb and hence the stance phase is shortened
  - Trendelenburg gait is caused by a neuromuscular problem (weak abductors)
  - Equinus gait, caused by tight Achilles tendon complex (idiopathic or neuromuscular). Hyperextension of the knee could be an adaptive manoeuvre
  - Circumduction gait, caused by a neuromuscular deficit. Can also be seen in the longer leg, or when dorsiflexion in the ankle is reduced due to pain.

Examination of the child should be with the above information in mind.

- Investigations:
  - Haematological: FBC, CRP
  - Ultrasonography of the hip
  - Plain radiographs of the hip or any particular area of concern
  - Bone scan
  - MRI

### Differential diagnosis

- Foreign body
- Trauma (stress fractures)
- Inflammatory (Irritable hip, arthritis)
- Infective (Osteomyelitis)
- Neuromuscular (cerebral palsy, congenital talipes equinovarus)
- Perthes disease: idiopathic limb length discrepancy
- Tumours

### Genu valgum and varum

- Is a usual cause for concern
- Most of them are physiological and spontaneously resolve
- Physiological genu varum (bow legs) is normally present until about 18 months of age
- Physiological genu valgum (knock knees) is at its worst at 3 years of age (it can be very dramatic needing strong reassurance)
- Other causes can be idiopathic, metabolic or syndromic.
- The intermalleolar and intercondylar distances help in quantifying the problem and monitoring its progress
- Treatment consists of reassurance, observation, correction of metabolic deficiencies (i.e. rickets)

and surgery

## Lower limb length discrepancy

- Can be true or apparent
- Causes:
  - Idiopathic
  - Congenital (hypo- or hyperplasia)
  - Vascular (arteriovenous fistula)
  - Trauma to the physis
  - Infection
  - Neurological

## Principles of management

- Assess if the discrepancy is progressive or static
- Calculate the projected discrepancy (PD) at skeletal maturity. On average, boys attain skeletal maturity at 16 and girls at 14
- Both of the above are done by measuring the limb lengths and plotting them on various graphs and charts (e.g. the Moseley straight line graph, Green–Anderson growth charts and Paley multiplier method)
- Mild PD, up to 1.5 cm, can be managed with shoe inserts
- PD between 1.5 and 5 cm can be treated by carrying out an epiphysiodesis of the longer leg. The timing of this procedure is very important, because it should be done while the child is still growing
- PD of 5 cm or more should be treated by lengthening the shorter leg

## 7. UPPER LIMB

### 7.1 Orthopaedic brachial plexus palsy

- Paralysis of the upper limb muscles noted at birth
- Incidence is 0.4 per 1000 live births
- Causes include pelvic dystocia, shoulder dystocia (upper cervical roots) and breech (lower cervical roots)
- There is a completely flail upper limb at birth, with full recovery in half the children, in a year's time
- The presence of Horner syndrome and a total plexus involvement are bad prognostic signs
- This is a C5–6 root problem, manifesting with weakness in the shoulder abductors and external rotators and elbow flexion and supination
- A rarer problem involving the lower roots can sometimes ensue. This affects the C7, C8 and T1 roots and presents as loss of sensation in the hand and loss of finger flexion
- A mixed palsy (even rarer) can sometimes occur
- Electromyograms can sometimes be helpful but they are not preferred because of the baby's age and

the discomfort that they can cause. It is better to follow these children clinically

- Treatment involves physiotherapy to keep the joints mobile and supple
- Failure of restoration of elbow flexion by 3 months necessitates referral for consideration of surgery

## 7.2 Trigger thumb

- Caused by nodular enlargement of the flexor tendon. This enlargement makes it difficult for the tendon to pass through the flexor sheath at certain points
- Smaller nodules can pass through with a trigger or snapping sensation
- Hence the clinical picture is of either a total or intermittent inability to extend the interphalangeal joint of the thumb
- Treatment consists of reassurance, observation and surgery (if symptoms persist)

## 8. INFECTION

### 8.1 Osteomyelitis

- Common in children but the incidence is decreasing
- In children it is usually acute and follows haematogenous spread (in the adult it usually follows direct inoculation)
- Pathophysiology – because the physis forms an avascular barrier there are a lot of end-arteries in the metaphyseal ends of the long bones. Blood flow is very slow there and this helps bacteria to settle and multiply there, thus causing infection
- Acute (diagnosis with symptoms for <2 weeks), subacute (symptoms for >2 weeks) and chronic (missed early diagnosis) phases are noted. This depends, to an extent, on the virulence of the affecting organism and the host immune response
- Clinical features – fever, pain in the affected limb, avoidance of using the limb, limping (90% affect the lower limb), reduction of adjacent joint movement (not as severe as septic arthritis)
- Previous history of flu-like illness should be elicited and questions about otitis, pharyngitis and impetigo must be asked
- Investigations include full blood count, erythrocyte sedimentation rate (ESR), CRP, blood cultures, plain radiographs (may be normal in acute osteomyelitis) and bone scan (may sometimes be needed to confirm diagnosis)
- MRI and ultrasonography may also be required. Occasionally single photon emission computed tomography (SPECT) scans may be required
- Differential diagnoses include septic arthritis, fractures, neoplasms and acute infarction episodes
- Complications include chronic osteomyelitis, pathological fractures, septic arthritis and growth arrests or physeal bars
- Common causative organisms – *Staphylococcus aureus* (most common), group B streptococci, *Escherichia coli*, *Haemophilus influenzae*, *Neisseria meningitidis*. The incidence of metacillin-resistant *S. aureus* (MRSA) osteomyelitis is increasing especially in the community
- Treatment should include antibiotics to cover the respective organisms. This should usually last for

6 weeks. CRP is a good investigation with which to monitor the progress of treatment

## 8.2 Septic arthritis

- Most commonly affected joints are the hip and the knee
- Peak age is 3 years but can affect virtually any age group
- Usually involves a single joint if it is an uncomplicated septic arthritis
- Pathophysiology – the cause is usually transient bacteraemia, direct inoculation or decompression of a juxta-articular osteomyelitis
- Clinical features:
  - Fever, irritable hip and limp; refusal to use the involved extremity
  - Painful limited range of motion
  - Effusion
  - A typical attitude of the limb (as the child tends to hold the limb with the joint in a position of maximal comfort)
  - Pseudoparalysis in the newborn should raise suspicions
- Investigations:
  - Full blood count, ESR, CRP (normal values do not necessarily rule out infection in this age group)
  - Blood cultures
  - Microscopy, culture and sensitivity of the joint aspirate
  - Plain radiographs
  - Ultrasonography
  - MRI and bone scan (can be normal if there is a tense effusion in the joint) may sometimes be required because diagnosis is often difficult
- Treatment:
  - Consists of early administration of antibiotics and drainage of the purulent effusion in the joint
  - Splintage may sometimes be required
- Prognosis is good if diagnosis is early and treatment is instigated immediately. Delay in treatment can lead to early secondary arthritis with significant post-septic sequelae
- Most common organisms:
  - Neonate – *S. aureus*, group B streptococci
  - Child <5 years – *S. aureus*, group A streptococci, *Streptococcus pneumoniae*
  - Child >5 years – *S. aureus*, group A streptococci
  - Adolescent – *S. aureus*, *Neisseria gonorrhoeae*
- Note atypical presentations – tuberculosis is on the increase in the western world so has a high index of suspicion

## 9. PAEDIATRIC SPINE

### 9.1 Scoliosis

- Prevalence is 0.5 to 3 per 100 (for curves between 10° and 30°)

- Generally girls are affected more commonly than boys (but this may change for different age groups)
- Three-dimensional deformity (lateral curve and rotational deformity)
- Studies show both X-linked and autosomal dominant inheritance
- Recent studies have shown that certain hormonal factors, such as melatonin, play an important part in the progression of this condition

## **Classification**

- It can be idiopathic, neuromuscular, congenital, hysterical, functional and mixed with other associations (mesenchymal, traumatic, osteochondrodystrophies, etc.)
- It can also be classified into: infantile (0–3 years), juvenile (3–10 years) and adolescent (>10 years)

## **Clinical features**

- Asymmetry of the shoulder
- Asymmetry of the top of the pelvis
- Adams forward bend test shows a rib prominence to the side of the curve
- Lateral deviation of the head is measured (from the natal cleft) by dropping a plumb line from the C7 vertebra
- Lower limb lengths should be assessed for true and apparent limb-length discrepancy
- Truncal shift should also be assessed
- Associated features, such as café-au-lait spots (neurofibromatosis), hairy patch in the lumbosacral area (spinal dysraphism) and joint laxity (connective tissue disorder) should be noted
- Full neurological examination of the lower and upper limbs should be carried out

## **Investigations**

- Plain radiographs of the whole spine – posteroanterior and lateral (standing views)
- MRI and CT may be indicated depending on the neurology present and to assess for any congenital bony anomalies

## **Treatment**

- Identify the curves that are more likely to progress (to be done by a paediatric spinal surgeon)
- Bracing (controversial in the UK but more commonly used in the USA)
- Surgery with or without spinal fusion
- Treat any intraspinal abnormalities such as syringomyelia or dysraphism before attempting curve correction

## **9.2 Kyphosis**



- Normal in the thoracic and sacral regions of the spine
- Between T5 and T12, an angle of 20–40° is considered normal; 40–50° is considered borderline normal; <20° is termed **hypokyphosis** and >50° is termed **hyperkyphosis**.

## Causes of kyphosis

Hyperkyphosis	Hypokyphosis
Congenital	Scoliosis
Neuromuscular	Iatrogenic
Postural	
Scheuermann disease	
Connective tissue disorders	
Metabolic	
Trauma	

## 10. FURTHER READING

- Herring JA (2002). *Tachdjians' Paediatric Orthopaedics*, 3rd edn. Philadelphia, PA: WB Saunders.
- Sillence DO, Rimoin DL (1978). Classification of osteogenesis imperfecta. *Lancet* **i**:1041–2.
- Staheli LT (2003). *Orthopaedic Secrets*, 2nd edn. Philadelphia, PA: Hanley & Belfuss.
- Staheli LT (2006). *Practice of Paediatric Orthopaedics*, 2nd edn. Philadelphia, PA: Lippincott Williams & Wilkins.

---

# Chapter 22

## Respiratory

*Rebecca Thursfield and Jane C Davies*

---

## CONTENTS

### 1. Anatomy and physiology

- 1.1 Embryology
- 1.2 Fetal and postnatal lung growth
- 1.3 Changes at birth and persistent fetal circulation
- 1.4 Control of respiration
- 1.5 Ventilation
- 1.6 Perfusion
- 1.7 Interpretation of oximetry and blood gases
- 1.8 Lung function testing
- 1.9 Respiratory defence mechanisms
- 1.10 Environmental influences on lung disease

### 2. Ear, nose, throat (ENT) and upper airway

- 2.1 Nose and sinuses
- 2.2 Cleft lip and palate
- 2.3 Ears
- 2.4 Throat
- 2.5 Larynx
- 2.6 Malacias
- 2.7 Sleep disordered breathing
- 2.8 Tracheo-oesophageal fistula
- 2.9 Gastro-oesophageal reflux
- 2.10 Cervical lymphadenopathy

### 3. Asthma

- 3.1 Pathophysiology
- 3.2 Drug treatment

### [3.3 Acute attack](#)

## [4. Cystic fibrosis](#)

### [4.1 Background](#)

### [4.2 Diagnosis](#)

### [4.3 Genetics](#)

### [4.4 Presentation and management](#)

### [4.5 New/emerging therapies](#)

### [4.6 Transplantation](#)

## [5. Other causes of bronchiectasis](#)

## [6. Bronchopulmonary dysplasia](#)

## [7. Infections](#)

### [7.1 Epiglottitis](#)

### [7.2 Tonsillitis](#)

### [7.3 Croup](#)

### [7.4 Tracheitis](#)

### [7.5 Bacterial pneumonias](#)

### [7.6 Empyema](#)

### [7.7 Bronchiolitis](#)

### [7.8 Viral pneumonia/Pneumonitis](#)

### [7.9 Tuberculosis and atypical mycobacterial infection](#)

### [7.10 Infections in the immunocompromised host](#)

## [8. Inhaled foreign body](#)

## [9. Pneumothorax](#)

## [10. Neuromuscular disorders](#)

### [10.1 Spinal cord](#)

### [10.2 Peripheral nerve](#)

### [10.3 Neuromuscular junction](#)

### [10.4 Muscle](#)

### [10.5 Respiratory failure](#)

### [10.6 Non-invasive ventilatory support](#)

## [11. Rare disorders](#)

### [11.1 Congenital disorders](#)

### [11.2 Acquired disorders](#)

## [12. Further reading](#)

---

# Respiratory

---

## 1. ANATOMY AND PHYSIOLOGY

### 1.1 Embryology

*In utero* development is divided into four stages.

#### **Embryonic – up to week 5**

- Lung bud grows out from the fetal foregut
- Single tube branches into two main bronchi

#### **Pseudoglandular – weeks 6–16**

- Airways grow by branching (out to terminal bronchioles)
- Cartilage and lymphatics appear from 10 weeks onwards
- Cilia appear
- Pulmonary circulation develops, arteries arising from the sixth branchial arches

#### **Canalicular – weeks 17–24**

- Conventional architecture of the lung appears
- Thinning out of distal cells in preparation for gas exchange
- Further development of arterial circulation, and appearance of venous system
- Surfactant synthesis begins
- Lung fills with fluid (lack of fluid at this and later stage, e.g. with renal agenesis, leads to pulmonary hypoplasia)

#### **Alveolar sac – weeks 24–40**

- Formation of the acinus (respiratory bronchioles, alveolar ducts and alveoli)
- Cell differentiation into type I and II pneumocytes
- **Type I:**
  - >90% of alveolar surface

- Major gas-exchanging surface
- **Type II:**
  - Thought to be the progenitor cell for type I cells
  - Produces surfactant which maintains surface tension and prevents alveolar collapse during respiration
  - Surfactant-associated proteins A and D (hydrophilic) involved mainly in innate immunity
  - Surfactant-associated proteins B and C (hydrophobic) important for surface tension

## 1.2 Fetal and postnatal lung growth

Factors affecting fetal lung growth and development include:

- Lack of amniotic fluid
- Glucocorticoids, thyroid hormones, other hormones increase maturation
- Pressure effects (e.g. compression from diaphragmatic hernia, or space-occupying lesion leads to hypoplasia)

Postnatally, lung development and growth continue for 7 years and may be adversely influenced by:

- Ventilation and oxygen toxicity
- Early infection (e.g. adenovirus, respiratory syncytial virus [RSV])
- Pressure effects of large, space-occupying lesion, e.g. lung cyst

## 1.3 Changes at birth and persistent fetal circulation

Vaginal delivery compresses the thorax, leading to expulsion of lung fluid and expansion of the lungs with the first breath. The increase in oxygen content leads to closure of the ductus arteriosus (which in fetal life diverts right ventricular blood away from the lungs into the systemic circulation), and the resultant increase in left atrial pressure (from increased pulmonary venous return) closes the foramen ovale. Thus, the right-sided pulmonary and left-sided systemic circulations become effectively separated. Persistent fetal circulation describes the situation where the pulmonary vasculature fails to relax, leading to ongoing right-to-left shunting of (deoxygenated) blood at the ductal and foramen ovale levels. Infants are severely hypoxic, mimicking the clinical picture of cyanotic congenital heart disease. Treatment includes ventilation with a high fractional inspired oxygen ( $FiO_2$ ), and administration of pulmonary vasodilators such as inhaled nitric oxide and prostacyclin.

## 1.4 Control of respiration

Inspiration is achieved largely by diaphragmatic effort with additional expansion provided by the intercostal muscles. At rest, expiration is largely passive, although this may become active upon exercise, or in children with respiratory disease. Expiration against a partially closed glottis both

prolongs this phase and raises airway pressure, leading to increased alveolar gas exchange. This is observed in the common sign of ‘grunting’ in infants with respiratory distress.

Respiratory drive is provided by both central (medulla) and peripheral (carotid body) chemoreceptors. In normal health, high  $\text{CO}_2$  leads to increased respiratory drive, although in chronic lung disease sensitivity may be blunted, and there is a dependence on hypoxia for this stimulus.

## 1.5 Ventilation

Air passes through the trachea, major bronchi and terminal bronchioles (anatomical deadspace) before reaching the sites of active gas exchange, the alveoli. In normal health, alveolar walls are thin (one cell thick) facilitating  $\text{O}_2$  and  $\text{CO}_2$  exchange. In diseases affecting the alveolus, gas exchange will be impaired, leading to an increase in respiratory rate in response to both a low  $\text{O}_2$  and a raised  $\text{CO}_2$ .

## 1.6 Perfusion

Perfusion is matched to ventilation via hypoxia-mediated pulmonary vasoconstriction, i.e. vascular constriction leads to diversion of blood flow away from poorly ventilated to well-ventilated areas, decreasing ventilation–perfusion ( $\dot{V}/\dot{Q}$ ) mismatch. Pulmonary arterial flow will be increased by vasodilatation in response to both high  $\text{O}_2$  and low  $\text{CO}_2$ , whereas pulmonary vasoconstriction, and thus hypertension, is exacerbated by hypoxia and hypercapnia.

## 1.7 Interpretation of oximetry and blood gases

### Pulse oximetry

- Non-invasive measure of oxygen saturation based on absorption of light by oxyhaemoglobin
- Prone to movement artefact and dependent on good pulse pressure
- Widely used, but caution required in interpretation, e.g. normal saturation in a child receiving supplemental  $\text{O}_2$  may lead to a false sense of security when there can still be significant respiratory compromise and hypercapnia
- Stable, mature values are reached by 6 months of age; normal values in awake children are 95–100% (for preterm infants) and 97–100% (for term infants and children)

### Blood gas measurement

- Arterial samples are rarely indicated in children outside the intensive care setting
- Capillary and venous samples are good surrogates for  $\text{PCO}_2$  and pH, but not  $\text{PO}_2$
- Transcutaneous measurements of both  $\text{O}_2$  and  $\text{CO}_2$  are possible, and end-tidal  $\text{CO}_2$  is also used in

the paediatric intensive care setting

- Normal ranges
  - pH 7.35–7.45
  - $PCO_2$  4.5–6.0 kPa
- Low pH: metabolic acidosis (normal or low  $PCO_2$ , low  $HCO_3^-$ , increased base deficit) or respiratory acidosis (raised  $PCO_2$ ; pH may be normalized by raised  $HCO_3^-$  if chronic)

## 1.8 Lung function testing

### Infants

Methods for testing lung function in infancy have been developed and are in use in the research setting, although they are not yet in widespread clinical use. In general, a sedated infant is fitted with a tightly fitted facemask. After either a tidal breath or, with some methodologies, an assisted inspiration, a jacket is rapidly inflated around the infant's chest, leading to forced expiration, from which flows and volumes can be measured.

### Older children

From the age of between 5 and 7 years, children will usually be able to perform standard lung function tests. The following values can be obtained:

**FVC** – forced vital capacity, is the total amount of air exhaled upon forced expiration.

**FEV<sub>1</sub>** – forced expiratory volume in the first second; gives a measure of large (and medium-sized) airway obstruction.

The ratio of these two values gives an indication as to the nature of an abnormality. Restrictive lung diseases such as fibrosis lead to reduction in both parameters, with preservation of the normal ratio (approximately 80%), whereas obstructive diseases (asthma, cystic fibrosis) lead to a greater reduction in FEV<sub>1</sub> and thus a reduced FEV<sub>1</sub>:FVC ratio.

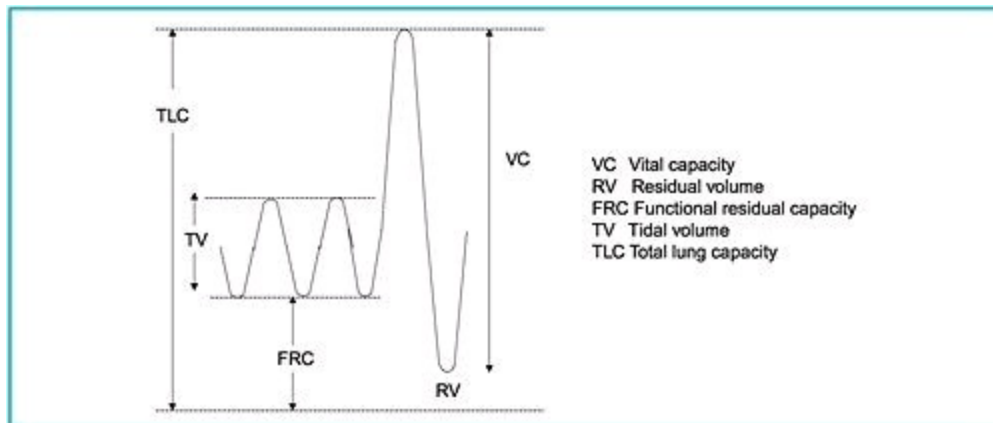
**FEF<sub>25–75</sub>** – forced expiratory flow between defined vital capacity (25% being empty) is a measure of flow at lower lung volumes, is non-effort dependent, and is thought to be a reasonable representation of small airway function. However, the coefficient of variation, even in healthy adults, is high.

**PEFR** – peak expiratory flow rate. Although useful as a home monitoring device in patients with asthma, it can be quite effort dependent and can underestimate significant small airway obstruction.

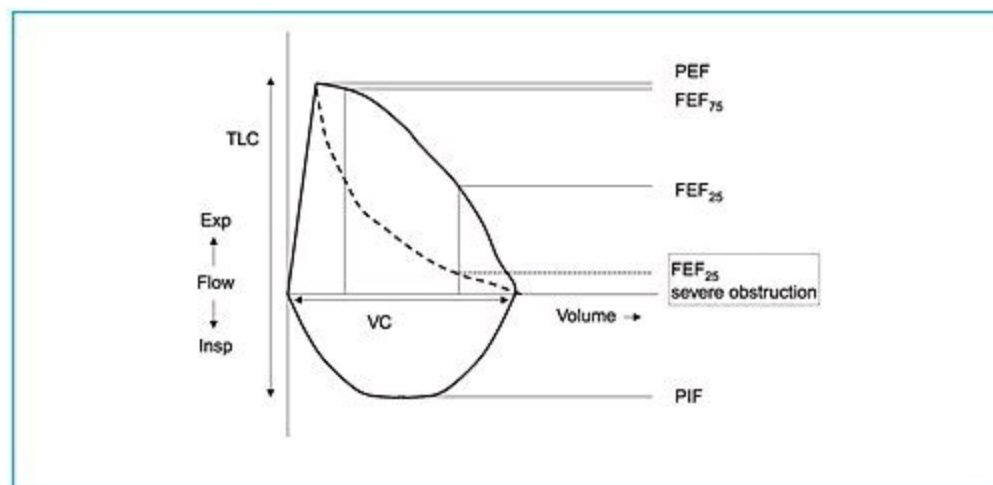
All of the above measurements can be obtained using a simple spirometer. For more complex measurements of lung volume, patients perform plethysmography, which involves sitting inside an airtight box.

**RV** – residual volume is the amount of air left in the lungs after maximal expiration. It is increased in diseases such as asthma because narrowed small airways prevent complete emptying of more distal lung and result in air trapping.

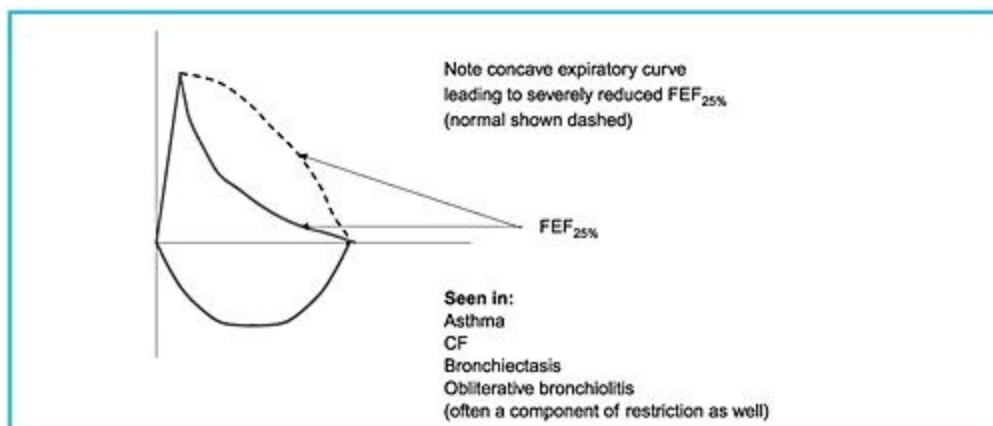
In addition to the above, the transfer factor for CO and corrected total lung CO (corrected for lung volume) give an estimate of the lung diffusion capacity. These measures are reduced in diseases where alveolae are abnormal and gas exchange is impaired, and increased in the presence of red blood cells which can absorb CO (e.g. pulmonary haemorrhage or haemosiderosis).



Lung volumes

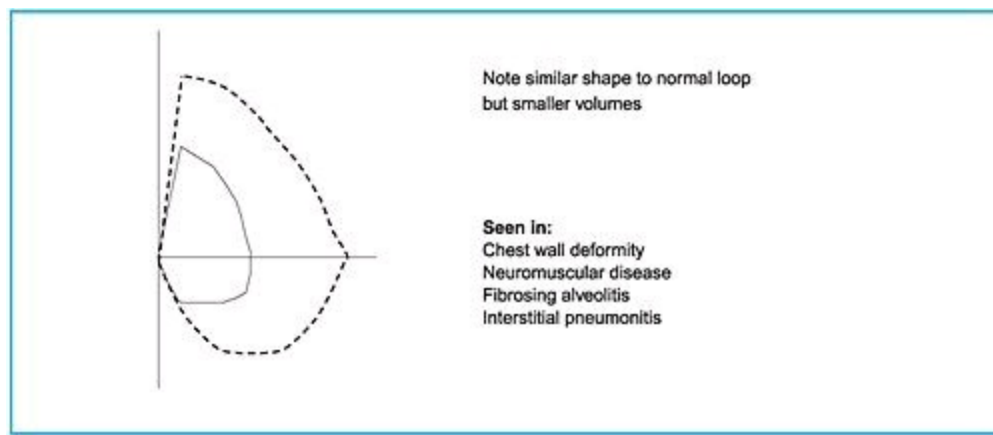


Flow–volume loop



Obstructive defect





Restrictive defect

## 1.9 Respiratory defence mechanisms

Pulmonary defences can be mechanical or immunological.

### Mechanical defences

- **Mucociliary clearance**, whereby cilia beat in a coordinated fashion bathed in a normal volume and composition of airway surface liquid, to bring inhaled particles to the throat where they are swallowed. Abnormal in primary ciliary dyskinesia (problem with ciliary microstructure) and cystic fibrosis (normal cilia but decreased airway surface liquid volume)
- Cough clearance

### Immunological defences

- Innate:
  - Phagocytosis by macrophages and neutrophils
  - Soluble factors including hydrophilic surfactant proteins A and D, lactoferrin, lysozyme, defensins
- Acquired:
  - Humoral: largely immunoglobulin A (IgA) upper airway, IgG lower airways
  - Cell mediated

## 1.10 Environmental influences on lung disease

- Cigarette smoke – antenatal effect on growing lung is now well established. Between 40 and 60% of British children are exposed to tobacco smoke at home. Passive smoking in children is associated with an increased risk of asthma, wheeze, otitis media and sudden infant death syndrome
- Aeroallergens
- Atmospheric pollutants – ozone, particulates, lead, sulphur dioxide and CO have all been shown to increase severity of asthma

## **2. EAR, NOSE, THROAT (ENT) AND UPPER AIRWAY**

### **2.1 Nose and sinuses**

#### **Choanal atresia**

Unilateral or bilateral. A congenital malformation occurring in approximately 1 per 60 000–70 000 births as a result of the failure of the breakdown of the buconasal membrane, leading to complete obstruction of the nostril(s). Bilateral choanal atresia presents immediately at birth (because the neonate is an obligate nose breather) with severe respiratory compromise and inability to pass a nasal catheter. Artificial oral airway is life saving and surgery is required. It is associated with other congenital defects, e.g. cardiac.

#### **Allergic rhinitis**

This presents as rhinorrhoea, sniffing, altered sense of smell (and taste),  $\pm$  itchy eyes and conjunctivitis. It may be either seasonal (usually triggered by pollens, grasses, etc.) or related to environmental allergens (e.g. house-dust mite, dogs, cats, horses). Often associated with a history of atopy in the child or family. Degree of disturbance to a sufferer of severe rhinitis is probably underestimated (problems with concentration, poor sleep quality, etc.). Management should include allergen avoidance and topical (nose  $\pm$  eyes) administration of corticosteroids or cromoglicate-based agents. In severe cases, oral antihistamines may be required. Children with allergic rhinitis may also have nasal polyps.

#### **Nasal polyps**

These occur in atopic children and in cystic fibrosis (CF – must consider CF diagnosis in any child with polyps). Children present with runny nose, nasal obstruction, decreased sense of smell and distortion of nasal shape. Polyps may respond to topical corticosteroids but are often difficult to treat, necessitating surgical removal. Recurrence post-surgery is unfortunately common.

#### **Epistaxis**

Nosebleeds are reasonably common in childhood. They are usually from the Little area on the septum and often triggered by nose picking. They are more common in inflamed/infected nose (e.g. allergic rhinitis/polyps). If recurrent/severe, it is essential to rule out a bleeding disorder, e.g. idiopathic thrombocytopenic purpura, haemophilia, leukaemia, or anatomical abnormality (e.g. haemangioma, telangiectasia). Pressure under the nasal bridge is usually adequate to halt bleeding. If severe, nose may need packing. Cauterization may be undertaken for recurrent episodes.

#### **Sinusitis**

Frontal sinuses are not aerated until the age of 3–5 years, so frontal sinusitis is not seen before this age. Later, it presents with headache/facial pain (made worse by coughing/bending down), nasal

congestion/discharge, concentration problems.

Sinusitis is associated with CF (almost 100% of adult patients have opaque sinuses so a radiograph is not very useful). It may also be associated with humoral immunodeficiency, e.g. IgA or IgG subclass deficiency.

Treatment involves decongestants and antibiotics; surgical drainage is required in a minority.

Complications (rare but serious):

- Orbital cellulitis
- Frontal osteomyelitis
- Meningitis/cerebral abscess
- Intracranial (including cavernous sinus) thrombosis

## 2.2 Cleft lip and palate

This is often now diagnosed antenatally on ultrasound scanning. It can be associated with Pierre Robin sequence (micrognathia and glossoptosis), other dysmorphic syndromes (e.g. Stickler syndrome, Edwards syndrome), or may occur in isolation, in which case prognosis is usually excellent. Certain antiepileptic medications are associated with increased incidence and there is some evidence of prevention with folic acid (as in spina bifida). Familial cases are not uncommon, making a genetic component very likely.

### Main problems

- **Cosmetic** – lip cleft is repaired early at approximately 2–3 months of age
- **Feeding:**
  - Special teats for bottles are available
  - Feeding is facilitated by a palatal plate if cleft is severe
  - There may be associated oropharyngeal incoordination and aspiration of feeds
  - Cleft palate surgery is usually performed by the age of 1 year
- **Speech and hearing:**
  - Often associated with frequent ear infections and glue ear
  - Large cleft can cause speech difficulties
- **Airway obstruction** – if due to Pierre Robin sequence some infants require a nasopharyngeal tube to maintain patency of the upper airway

## 2.3 Ears

### Acute otitis media

Caused by both viruses and bacteria, this is experienced frequently, especially by young children. It

generally presents with otalgia  $\pm$  fever and discharge. Examination typically reveals an inflamed, bulging eardrum with dull tympanic reflection due to middle-ear fluid. Controversy exists as to the need for and the optimal timing of antibiotics, but a frequently used management strategy is to treat if symptoms persist beyond 3 days.

## **Chronic otitis media**

Chronic otitis media (glue ear) is a major cause of hearing problems and speech delay; it results from the accumulation of thick secretions in the middle ear and recurrent acute infections. It may be associated with adenoidal hypertrophy; adenoidectomy may improve symptoms. Long-term antibiotics are not very useful.

Insertion of grommets to release the fluid and pressure is often performed. Normally they are extruded spontaneously after about 6–9 months. Studies have suggested that swimming is not harmful to a child with grommets (but they should not dive).

## **Deafness**

Deafness can be conductive or sensorineural.

### **Conductive deafness**

- Most common of the two types, detected in up to 3–4% of schoolchildren; often mild
- Almost always secondary to chronic otitis media
- Preservation of bone conductance with diminished air conductance

### **Sensorineural deafness**

- Less common; 0.2–0.3% of children and more likely to be severe
- Caused by either cochlear or neuronal damage (may be iatrogenic, e.g. aminoglycoside toxicity)
- Equal impairment of both bone and air conductance

### **Causes of sensorineural deafness**

- Genetic – associated with dysmorphic syndromes
- Congenital infections (TORCH group – **t**oxoplasmosis, **o**ther infections, **r**ubella, **c**ytomegalovirus, **h**erpes simplex)
- Birth asphyxia
- Severe jaundice
  - CNS infection:
  - Post-meningitis
  - Encephalitis
  - Cerebral abscess
- Aminoglycoside toxicity
- Head injury

Treatment:

- Hearing aids may be useful if there is some preservation of hearing
- Cochlear implants in selected cases
- Multidisciplinary approach

## **Mastoiditis**

This has become rare with the use of antibiotics to treat acute otitis media. It results from the breakdown of the bony walls of mastoid air cells, secondary to ongoing bacterial middle-ear infection. It presents with high fever, toxicity, irritability, marked focal tenderness over the mastoid process, discharging ear  $\pm$  deafness. If early in the process, it may respond to parenteral antibiotics; in more severe cases, surgical intervention may be required.

## **2.4 Throat**

### **Adenotonsillar hypertrophy and airway obstruction**

Adenotonsillar hypertrophy is common in childhood, although most cases require no specific treatment and will resolve with age. More severe cases are associated with certain disease groups, e.g. sickle-cell anaemia and human immunodeficiency virus (HIV) infection.

Symptoms either relate to recurrent infections or airway obstruction. Obstruction may be obvious to parents (snoring  $\pm$  apnoeic pauses, mouth breathing), or may present with right heart failure and cor pulmonale if not recognized until late. Polysomnography may reveal obstructive episodes (increased chest excursion with diminished airflow  $\pm$  hypoxia and hypercapnia if severe), although in the majority of cases diagnosis can be made on the history.

Management is by surgical removal in selected cases.

### **Oropharyngeal incoordination and aspiration**

Swallowing is a complex mechanism requiring intact anatomy and neuromuscular coordination. Diseases affecting either pathway can lead to saliva and food/drink entering the respiratory tract.

It should be considered as a cause of respiratory symptoms especially in at-risk groups such as:

- Preterm babies with immature swallowing mechanisms
- Central nervous system (CNS) disease, e.g. cerebral palsy
- Anatomical abnormality, e.g. cleft palate/larynx
- Any cause of generalized hypotonia especially with bulbar involvement

Aspiration with intact swallow is also seen with severe gastro-oesophageal reflux and tracheo-oesophageal fistula.

Symptoms may be overt (choking and coughing with feeds) but are often absent. Leads to recurrent wheeze and aspiration pneumonias. It is diagnosed on video-fluoroscopy. Management depends on cause but severe cases may require surgical intervention.

## 2.5 Larynx

**Laryngeal web** is rare and if complete is obviously incompatible with life. More commonly, it results in partial laryngeal obstruction, respiratory distress and stridor. **Laryngeal cleft** is very rare and occurs due to failure of closure of the tracheo-oesophageal septum at 35 days of embryonic development. It presents with aspiration, choking, episodes of cyanosis  $\pm$  apnoea. Both require surgical repair.

**Haemangioma** of the larynx presents with airway obstruction, cough or stridor. It may coexist with cutaneous haemangiomas so examine the child completely. It is visible as a soft mass on instrumentation of the airway and may bleed copiously if traumatized or biopsy is attempted. Topical application of adrenaline may be life saving in such a situation.

**Papillomatosis** is a rare cause of hoarseness if affecting the larynx. It may present with stridor or barking cough.

## 2.6 Malacias

Any tubular component of the respiratory tract may be malacic (floppy).

It results in partial or complete collapse on inspiration although patency is well maintained on expiration.

- Presentation;
  - Inspiratory stridor, respiratory distress
  - Apnoea
  - Feeding problems
  - Recurrent croupy episodes
- Diagnosis can be confirmed on laryngo-/bronchoscopy (although it is usually possible clinically)
- Mild cases (the majority) become less severe with growth
- Severe cases may benefit from aortopexy or airway stenting

## Causes of stridor

### Common

Croup  
Laryngo-/tracheomalacia  
Subglottic stenosis/granuloma (post-intubation)

Vascular ring  
Inhaled foreign body (if large and proximally lodged)

## Rarer

Epiglottitis (much less common since Hib [*Haemophilus influenzae* type b] immunization)  
External tracheal compression  
Mediastinal mass, e.g. lymphoma/leukaemia  
Tuberculous lymphadenopathy  
Enlargement of heart/great vessels associated with congenital cardiac malformation  
Laryngeal web  
Haemangioma, papillomatosis  
Vocal fold palsy  
Vocal fold dysfunction  
Hypocalcaemia

## 2.7 Sleep-disordered breathing

This covers a spectrum of problems, ranging from snoring through to hypoxia/hypercapnia leading to pulmonary hypertension and cor pulmonale. It may be related to local (e.g. adenotonsillar hypertrophy) or systemic (e.g. neuromuscular) disease. Take a careful history. Ask specifically about pauses in breathing signalling sleep apnoea. It may lead to disrupted sleep/nocturnal enuresis/daytime somnolence/morning headaches (high CO<sub>2</sub>)/underachievement at school. Definitive diagnosis on polysomnography (see [Section 10.4](#)). Treatment is tailored to cause.

## 2.8 Tracheo-oesophageal fistula

Failure of normal development of the primitive foregut leads to a fistula connecting the oesophagus and trachea with or without oesophageal atresia.

Oesophageal atresia presents in the immediate neonatal period with vomiting, choking (± an absence of gas in the abdomen, depending on the position and size of the fistula). Confirmation is obtained by attempted passage of a nasogastric tube. This may exist as part of the VACTERL constellation (vertebral, **a**nal, **c**ardiac, **t**racheo-oesophageal fistula, **e**ars, **r**enal, **l**imb).

Tracheo-oesophageal fistula without oesophageal atresia will often present later. At its most obvious, the child may choke with feeds, but equally the history may be one of recurrent chest infections or wheeze. Diagnosis is made on a tube oesophago-gram (injection of radio-opaque dye into the oesophagus under pressure to force open a small fistula). It is often missed on bronchoscopy, particularly flexible bronchoscopy.

Treatment for both conditions is surgical.

## 2.9 Gastro-oesophageal reflux

There is increased risk of gastro-oesophageal reflux in preterm infants, in neurologically impaired infants and, probably, in severe chronic lung disease. It may also exacerbate lung problems such as asthma, which makes differentiating cause and effect difficult. The most commonly used test for diagnosis is the pH probe. Normal reflux index (percentage of time pH in lower oesophagus  $<4$ ) is 4% in older children but probably up to 10% in infants. In some centres gastro-oesophageal reflux disease (GORD) is diagnosed with an impedance study; this detects all reflux events, compared with a pH study which detects only acid reflux. It also has the advantage of being able to quantify how far up the oesophagus the child is refluxing. However, interpretation is time-consuming, requires expertise and there are no standardised data. It is only carried out in specialised centres. Reflux may lead to episodes of aspiration (may be silent), which if recurrent result in irreversible lung damage. Medical treatment is with combination of antacid (H<sub>2</sub>-receptor blocker or proton pump inhibitor) and prokinetic, e.g. domperidone. If unsuccessful, a Nissen fundoplication may be required.

## 2.10 Cervical lymphadenopathy

The most common cause is upper respiratory tract infection. It usually resolves spontaneously, although small lymph nodes may persist into adult life. If chronic or severe, alternative diagnoses should be considered, e.g. infectious mononucleosis, dental disease, non-tuberculous mycobacteria, cat-scratch disease (*Bartonella henselae*). If generalized, consider alternative diagnoses and look for supportive signs of malignancy (e.g. lymphoma), HIV, Kawasaki disease.

# 3. ASTHMA

## 3.1 Pathophysiology

This is a chronic inflammatory disease of the airways with a well-recognized genetic component in which many cells are involved, including eosinophils, lymphocytes and mast cells. Airway inflammation leads to airway oedema, and hyperreactivity resulting in reversible bronchoconstriction.

If left untreated, the inflammatory changes may eventually become chronic and irreversible, a process termed ‘airway remodelling’.

From both laboratory and epidemiological studies, a protective role for infection against the subsequent development of asthma has been demonstrated, e.g. there is a decreased incidence in children with older siblings or raised on farms.

T-lymphocyte populations are biased towards a T-helper (Th<sub>2</sub>) cell phenotype (interleukin [IL]-4 and IL-5 secretion, involved in IgE production), as opposed to the Th<sub>1</sub> phenotype which is more commonly found in response to infection.



# Symptoms

Symptoms may be classic wheeze and dyspnoea, or a cough variant. They are often worst at night or in the early morning.

# Triggers

- Viruses
- Allergens (e.g. house-dust mite, cats, dogs)
- Cold air
- Cigarette smoke
- Exercise
- Stress/emotional

## 3.2 Drug treatment

# Management

Management should include:

- Identification and avoidance of precipitating factors (e.g. house-dust mite, pets, cigarette smoke)
- Education – importance of long-term prophylaxis
- Recognition and management of acute attack (written plan where appropriate)

## British Thoracic Society guidelines for asthma management

- Step 1 – short-acting bronchodilators as needed
- Step 2 – addition of low-dose inhaled steroid or other preventer drug if steroid inhaler cannot be taken
- Step 3 – >5 years: long-acting bronchodilator, increase steroid dose, and if still not controlled slow-release theophylline or leukotriene antagonist  
– <5 years: addition of leukotriene antagonist
- Step 4 – further increase of steroid dose
- Step 5 – regular oral corticosteroids; referral to respiratory paediatrician

Before stepping up treatment, drug compliance should be checked. Guidelines recommend stepping down treatment when control is achieved, i.e. aim for best control on lowest dose.

## Treatment options beyond step 5 (very rare and needs to be under subspecialist care)

- Continuous subcutaneous terbutaline

- Anti-IgE monoclonal antibody (omalizumab)
- Alternative immunosuppressive drugs:
  - Methotrexate – can cause bone marrow suppression, liver cirrhosis, GI toxicity (look for mucositis); requires full blood count (FBC), liver function tests (LFTs) and renal function monitoring
  - Azathioprine can cause bone marrow suppression – requires FBC monitoring
  - Ciclosporin – can cause gum hypertrophy, hypertrichosis, hypertension, leukopenia, renal toxicity
- Monitor levels, liver and renal function, and BP

## Inhaler devices

You should know how to demonstrate each device. It is very important to choose an inhaler that is suitable for the child.

Inhaler devices	
Large volume spacers	Used with metred-dose inhalers Best lung deposition Used with mask in young age group, and with mouthpiece when old enough to form a seal Static charge reduces lung delivery: leave to dry after washing – do not dry with towel
Smaller spacers	Single puffs best administered individually For example, AeroChamber; more portable and versatile, although delivery with some not quite as good
Dry powder inhalers	Children (usually around 4–7 years) who can: <ul style="list-style-type: none"> <li>• form a seal with their lips</li> <li>• hold their breath</li> </ul> Includes Turbohaler, Diskhaler, Acuhaler, etc.

Metred-dose inhalers have poor lung deposition (most of the drug remains in the mouth and pharynx) and are not to be recommended for use alone.

Long-acting bronchodilators are useful to gain control instead of increasing steroid dose and in exercise-induced asthma. Now available in combination delivery devices with corticosteroid, which may improve compliance.

## 3.3 Acute attack

Signs of severity:

- Inability to talk in sentences
- Tachypnoea/tachycardia
- Inter-/subcostal recession
- Use of accessory muscles of respiration
- Quiet or silent chest (poor air entry)
- Pulsus paradoxus
- Cyanosis (very late sign – beware)

In the presence of tachypnoea, a normal CO<sub>2</sub> level indicates a severe attack

## Management of acute severe asthma

- Oxygen
- Bronchodilator via a spacer device has been shown to be as effective as, if not more so than, via nebulizer; can be given continuously. If unsuccessful, give intravenous salbutamol with cardiovascular monitoring. Watch K<sup>+</sup>
- Aminophylline:
  - Give loading dose slowly
- Systemic (usually intravenous) steroids
- Intravenous magnesium sulphate shown to be efficacious in meta-analyses
- If respiratory support is required:
  - Lowest possible inspiratory pressures
  - Short inspiratory time; long expiratory time
  - Minimal/no positive end-expiratory pressure to reduce air trapping

## Causes of wheeze in childhood

### Common

- Virus-associated recurrent wheeze
- Acute viral infection, e.g. RSV, adenovirus
- Asthma
- Gastro-oesophageal reflux (and aspiration syndromes)
- Cystic fibrosis
- Inhaled foreign body

### Rare

- Distal bronchomalacia
- Obliterative bronchiolitis
- Bronchiectasis

## 4. CYSTIC FIBROSIS

### 4.1 Background

Cystic fibrosis (CF) is the most common lethal recessive disease of white people, with a carrier frequency of 1:25, leading to disease in 1:2500 births of white babies (>9000 patients in the UK). Previously regarded as a disease of childhood, increases in survival have swelled the adult CF population. Median survival for a child born today is estimated at 40 years.

The gene responsible encodes the CF transmembrane conductance regulator (*CFTR*) and is on chromosome 7. The primary function of *CFTR* is as a chloride ion channel, but it also inhibits the epithelial sodium channel. CF respiratory epithelium therefore fails to secrete chloride ions (fails to absorb in the sweat gland, hence high sweat electrolytes), and hyperabsorbs sodium ions and thus H<sub>2</sub>O, dehydrating the airway surface. Secretions are viscid, impairing mucociliary clearance and thus host defence.

*CFTR* is now known to have other functions (related to the transport of other substances, e.g. bicarbonate, and receptors for bacteria) but they are controversial.

Other organs affected for similar reasons include the gut, pancreas, liver and reproductive tract.

## 4.2 Diagnosis

### Newborn screening (NBS)

- All children in the UK have been screened for CF as part of the newborn screening programme since October 2007
- Immunoreactive trypsin (IRT) is raised in the first 6 weeks of life in infants with CF
- Infants with IRT >99.5th centile on their Guthrie test have *CFTR* mutation analysis
- As with most screening programmes, there will be some false negatives (approximately 3–6%) so CF diagnosis still need be considered in screened children if symptoms are suggestive

### Sweat test

- ‘Gold standard’: values of chloride ions >60 mmol/l are diagnostic (40–60 borderline; many consider cut-off to be 30, particularly for infants)
- Traditionally the test required at least 100 mg sweat, but newer methods (e.g. macroduct) require less
- Cases of CF with normal sweat electrolytes have been reported, so if there is a high suspicion for disease a normal sweat test does not rule out a diagnosis of CF.

### Possible causes of false-positive sweat test:

- Technique (evaporation leads to increased concentration and decreased volume)
- Eczema/dermatitis/ectodermal dysplasia
- Severe malnutrition or dehydration
- Untreated hypothyroidism/panhypopituitarism
- Adrenal insufficiency
- Glycogen storage disease/mucopolysaccharidosis
- Glucose-6-phosphate dehydrogenase deficiency
- Fucosidosis
- Nephrogenic diabetes insipidus

# Genetic testing

See [Section 4.3](#).

## Nasal potential difference

Mostly used for research purposes but useful in grey cases. Technically challenging in children.

## 4.3 Genetics

Over 1800 mutations in *CFTR* have been identified to date. They fall into five classes. The most common is *Phe508del* (previously called *F508*), a class II mutation that leads to defective protein folding and thus failure to reach the apical membrane. There is a relationship between pancreatic status and genotype, but correlations for lung disease have been poor to date. Except in rare cases, it should not be used to provide prognosis.

Most clinical laboratories test for up to 34 of the most common mutations (which detects >90% of cases in white individuals). This is useful for antenatal testing of subsequent pregnancies.

## 4.4 Presentation and management

### Neonatal

Most common presentation is now a positive NBS result. Some neonates present before screening with meconium ileus, bowel obstruction secondary to thick inspissated gut contents. It may be antenatal and be visible as hyperechogenic bowel on an ultrasound scan or lead to meconium peritonitis. It often requires surgery, although very mild cases occasionally managed medically, e.g. with Gastrografin.

### Rarer early presentations

- Pseudo-Bartter syndrome (hypochloraemic, hypokalaemic alkalosis)
- Hypoalbuminaemia, oedema, anaemia
- Bleeding from vitamin K deficiency
- Haemolytic anaemia (vitamin E deficiency)

### Pulmonary

Lungs are thought to be normal at birth. Early symptoms such as cough, frequent chesty episodes and wheeze may be missed or labelled 'viral infections'. Early infection is with a narrow range of organisms:

- ***Staphylococcus aureus*** – most children in UK receive long-term prophylaxis
- ***Haemophilus influenzae***
- ***Pseudomonas aeruginosa*** – up to 80% of CF patients are chronically infected by the time they reach adolescence. Bacteria become mucoid, forming biofilms and are more difficult to eradicate when chronic. Treat with long-term nebulized antibiotics (colomycin or tobramycin/TOBI). Newer nebulisers, e.g. e-flow and i-Neb, shorten the duration of nebulized antibiotics from 20 min (with conventional nebulisers) to less than 5 min. Intermittent courses of intravenous antibiotics (always at least two) are required for some. Macrolide antibiotics are in more common use now. Shown to improve lung function, although mechanism of action unclear; may be anti-inflammatory
- **Allergic bronchopulmonary aspergillosis (ABPA)** – presents with dry cough, wheeze, variable infiltrates on chest radiograph. Diagnosed with high IgE, raised radioallergosorbent test (RAST) and precipitins. Skin-prick testing may be helpful. Treated with steroids ± itraconazole, which may need to be prolonged
- ***Burkholderia cepacia*** – Gram negative, often highly resistant. Meropenem may be useful. Associated in approximately 20% with life-threatening septicaemia ('cepacia syndrome'); patient-to-patient spread is well-documented (segregation vital)
- ***Stenotrophomonas maltophilia*** – an emerging pathogen; there is conflicting evidence on whether it leads to significant deterioration
- **Atypical mycobacteria** – quite common. May be an incidental finding. Treat if symptomatic, persistent or patient is immunosuppressed, e.g. on steroids. *Mycobacterium abscessus* particularly likely to be associated with increased disease severity

Airway inflammatory response is excessive. End-result of infection/inflammation is bronchiectasis (upper lobes common), chronic sputum production, clubbing and hypoxia. May present with asthma-like symptoms (consider CF in cases of difficult/atypical asthma). May have haemoptysis (high bronchial arterial flow and, if severe, embolization). Ninety per cent of patients die of respiratory failure.

## Other treatments for lung disease

Mainstay of treatment is physiotherapy (regular – even when patient is well!) and regular exercise. Consider bronchodilators if responsive. Many patients are on inhaled steroids (evidence lacking).

Mucolytics: given to aid sputum clearance with physiotherapy because in CF these can be thick and difficult to clear

- **Recombinant human DNase;**
  - Degrades viscous neutrophil-derived DNA
  - Nebulized once daily, at least 1 hour before physiotherapy
  - Very expensive (£7500/patient per year)
- **Hypertonic (7%) saline:**
  - Nebulized twice daily, just before physiotherapy
  - Can cause bronchoconstriction, so salbutamol may be given before saline

# **Extrapulmonary involvement**

## **Pancreas**

### *Exocrine insufficiency*

- Presents with steatorrhoea and faltering growth
- Low stool elastase, high 3-day faecal fat
- Treat with pancreatic enzyme supplements (e.g. Creon)
- Fat-soluble vitamin supplementation
- Nutritional supplements if required
- Gastrostomy and supplemental nutrition if severe weight problems

### *Endocrine problems*

- CF-related diabetes
- More common in older children (8–15%):
  - Insidious, non-specific onset
  - Ketoacidosis is extremely rare (residual pancreatic function)
  - Usually require insulin. Some evidence that early use of low-dose insulin in pre-diabetic phase may protect lung function
- Carries poorer prognosis, especially in females

## **Gastrointestinal tract**

- Distal intestinal obstruction syndrome (previously called meconium ileus equivalent):
  - Rehydrate and administer Gastrografin, Klean-Prep, etc.
  - Attention to dietary fibre and enzymes
- Hepatic cirrhosis:
  - Ursodeoxycholic acid may be useful

## **Nose**

- Polyps (up to 30%): topical steroid or surgery – often recur

## **Sinusitis**

- Common – caused by obstruction
- Same causative organisms as lungs

## **Infertility**

- 99% males (obstruction and abnormal development of vas deferens)
- Females subfertile, but many successful pregnancies. Pulmonary health may be severely affected during pregnancy – need careful monitoring

## **Arthritis**

- Probably immune complex mediated
- Correlates with pulmonary function tests

## **Vasculitis**

- More common in older patients

## **Osteoporosis**

- More common with increasing age and severity of lung disease; also long-term steroid use. Many clinics monitor using bone densitometry

## **4.5 New/emerging therapies**

### **Gene therapy**

- Still at clinical trial stage
- Liposomes or recombinant viral vectors used as vectors

### **Anti-infectives**

- Dry powder antibiotics are currently in phase 3 clinical trials; may improve quality of life by reducing treatment burden
- AZLI (nebulized aztreonam)

### **CFTR modulation**

- Oral medications aimed at correcting the defective CFTR protein; these drugs are class specific
- A drug for class III mutations (VX-770; *CFTR* potentiator) has shown improvement in lung function and weight compared with placebo in phase 2 and 3 trials
- A new drugs for class I (premature stop mutations – *PTC124*) in phase 3 clinical trials
- Others directed at class II mutations are currently at earlier research stages

### **Ant-inflammatory**

- Ibuprofen:
  - Slows reduction in lung function but has side effects
  - Not in widespread use in the UK
- Novel drugs and drugs already in existence for other uses (such as sildenafil and acetylcysteine) are undergoing clinical trials to assess their benefit for airway anti-inflammatory drugs.
- Caution: some inflammation may be helpful. Complete abrogation of inflammatory response could lead to increased infective problems

## **4.6 Transplantation**



Heart–lung or bilateral lung transplantations are performed, limited by the number of organs available. More recently, living-related donors have been used; currently there is no advantage but this will possibly improve with further experience.

Psychological issues are of major importance.

### **Possible contraindications (vary slightly with different centres)**

- Long-term use of high-dose steroids
- Multiresistant organisms
- Previous thoracic surgery
- Lack of family support or psychological issues
- Severe osteoporosis

### **Post-transplantation problems**

- Prolonged immunosuppression and infection
- Obliterative bronchiolitis is common

## **5. OTHER CAUSES OF BRONCHIECTASIS**

Symptoms/signs are as for CF depending on severity. It may be visible on chest radiograph but computed tomography (CT) is more sensitive. Bronchography is no longer used.

### **Primary ciliary dyskinesia**

Previously called ‘immotile cilia syndrome’, this is an autosomal recessive problem (several genes probably involved). Rare: 1 per 15 000 births.

#### **Presentation**

- Neonatal respiratory distress, rhinorrhoea
- Recurrent lower respiratory tract infections possibly leading to bronchiectasis
- Sinus disease
- Glue ear – often does not respond well to grommets
- 40% have dextocardia ± abdominal situs inversus (Kartagener syndrome)
- Male infertility (female subfertility)

#### **Diagnosis**

- Nasal brushing for ciliary beat frequency (normal >10 Hz), assessment of beat coordination and structure (electron microscopy)
- Low exhaled/nasal nitric oxide

## Genetic testing

- Mutations in two genes (*DNAI1* and *DNAH5*) identified in about 40% of families with primary ciliary dyskinesia

## Treatment

- Physiotherapy
- Antibiotics
- ENT and hearing assessment
- Genetic counselling

## Post-infection

Classically occurs after pertussis, although may also follow measles. May occur after severe infection with any organism.

## Post-airway obstruction

- Highlights importance of early detection and removal of foreign bodies (see [Section 8](#))
- Tuberculosis – obstructive lymphadenopathy

## Recurrent infection

For example, immune deficiency (see [Section 7.9](#)).

## Recurrent aspiration

### *Idiopathic*

This explains up to 60% of cases but other causes must be excluded.

### *Congenital*

Rare.

## 6. BRONCHOPULMONARY DYSPLASIA

This is chronic lung disease resulting from premature delivery, surfactant deficiency and neonatal artificial ventilation.

Various definitions exist, all including the requirement for O<sub>2</sub> at 28 days.

Other aetiological factors include:

- Birth asphyxia

- High-concentration O<sub>2</sub> administration
- Fluid overload
- Infection
- Vitamin A deficiency – antioxidant effects

Of these, barotrauma from ventilation and oxygen toxicity is the most important. Centres using non-invasive ventilation as the first-line therapy (e.g. nasal continuous positive airway pressure [CPAP]) have a lower incidence of bronchopulmonary dysplasia.

Incidence is reduced greatly by both antenatal steroids (increases lung maturation and surfactant production) and exogenous surfactant. (For further details see [Chapter 17](#).)

## Treatment

- Long-term O<sub>2</sub>
- Corticosteroids
- Diuretics and fluid restriction may be useful
- Immunization including flu and Pneumovax
- Consider use of palivizumab (see [Section 7.7](#))
- Aggressive treatment of infections
- Bronchodilators may be useful in wheezy cases
- Consider and treat coexisting gastro-oesophageal reflux (immature swallow, reduced muscle tone, prolonged intubation all increase risk)

## Longer-term complications

- Reactive airway disease (e.g. risk of severe disease with RSV)
- Complications of intubation (e.g. subglottic stenosis, granulation tissue, tracheomalacia)
- Gastro-oesophageal reflux
- Pulmonary hypertension and cor pulmonale
- Growth and nutritional delay
- Neurodevelopmental disability

## 7. INFECTIONS

### 7.1 Epiglottitis

This is usually caused by *Haemophilus influenzae* type b. It is rare since introduction of the Hib vaccine. Presents with acute-onset stridor, fever and anxiety in the child.

Do not examine throat (may precipitate fatal airway obstruction)

Do not take radiograph (although appearances may be diagnostic, wastes time and is dangerous)

Do not upset child, e.g. taking blood, lying flat

If suspected – urgent general anaesthesia, visualization of upper airway and intubation. Rarely need tracheostomy. Bacterial swabs at intubation. Treat with intravenous third-generation cephalosporin.

## 7.2 Tonsillitis

Acute tonsillitis is common and self-limiting in childhood. Presentation may be non-specific in the small child, e.g. irritability, refusal of feeds, fever, febrile convulsion. Older child usually complains of sore throat. Bacterial and viral causes (commonly adenovirus, rhinovirus,  $\beta$ -haemolytic streptococcus); exudate does not imply bacterial cause.

### Indications for tonsillectomy

- Recurrent severe attacks of tonsillitis
- Tonsillar hypertrophy leading to airway obstruction/sleep-disordered breathing
- Associated eustachian tube obstruction with hearing impairment
- Recurrent otitis media associated with adenotonsillar infection

## 7.3 Croup

- Viral laryngotracheobronchitis – parainfluenza virus, influenza virus, RSV, rhinoviruses
- Common between 6 months and 5 years of age; more common in boys than girls
- Barking cough and stridor
- Child not usually toxic; may have low-grade fever
- No evidence in support of humidification
- Good evidence for a role for steroids: oral single dose (dexamethasone used in most studies) and inhaled budesonide effective and no good evidence to support one over the other
- Nebulized adrenaline will help in acute situation but effect is short-lived
- Severe cases may require intubation and ventilation
- May be recurrent

## 7.4 Tracheitis

- Presentation as for croup
- Viral (same as croup) and bacterial (*Staphylococcus aureus* and *Haemophilus influenzae*) aetiologies
- Bacterial cases often more toxic
- Severe cases may require intubation

## 7.5 Bacterial pneumonias

### Presentation

Variable depending on severity

- Cough
- Tachypnoea  $\pm$  other signs of respiratory distress (nasal flaring, grunting, use of accessory muscles)
- Fever
- Non-specific irritability/vomiting in younger infant
- Hypoxia
- Chest radiograph: often patchy shadowing in infant and more commonly lobar consolidation in older child

### Aetiology

- *Pneumococcus* sp. is the most common causative organism
- With increasing age, *Mycoplasma* spp. are more prevalent
- *Staphylococcus aureus* is associated with lung abscess (both staphylococci and streptococci may follow varicella virus infection)
- Rarely *H. influenzae*, streptococci, *Klebsiella* sp. (remember most pneumonias are viral in younger child)

### Management

- Mild cases can be diagnosed clinically and treated with oral antibiotics out of hospital
- More severe cases – cultures (sputum if available, upper airway secretions, blood):
  - White blood cell count and differential and C-reactive protein are useful for monitoring response to treatment (but do not differentiate well between bacterial and viral infections)
  - Intravenous antibiotics
  - Hydration (see below)
  - O<sub>2</sub> therapy if required
- Rarely, severe cases will require respiratory support

### Complications

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is common. It leads to fluid retention and thus hyponatraemia, which if severe can lead to cerebral oedema and convulsions. Monitor electrolytes and osmolality (serum and urine). Management is by fluid restriction and NOT by administration of sodium.

## 7.6 Empyema

Collection of pus in pleural space resulting from spread of infection from lung tissue. Presents with signs of pneumonia plus unilateral decreased air entry, dull percussion note. Patient often has scoliosis toward the affected side  $\pm$  mediastinal shift. Fluid demonstrated on chest radiograph. Ultrasound may confirm presence of loculation or fibrin strands.

## Management

- Requires drainage (not just aspiration)
- Intrapleural urokinase may assist recovery by breaking down fibrinous material to facilitate drainage
- Intravenous antibiotics
- Surgery
  - Decortication/video-assisted thoracic surgery (VATS)
  - Offers no advantage over drain + urokinase in the majority of cases

## Complications

- Bronchopleural fistula
- Lung abscess
- SIADH

## Other causes of pleural effusion

- Tuberculosis
- Chylothorax (especially post-surgery from thoracic duct ligation)
- Congestive heart failure
- Hypoalbuminaemia (with peripheral oedema, e.g. nephrotic syndrome)
- Malignancies (rare)
- Blood in pleural space will have similar chest-radiograph appearance, e.g. post-trauma

## 7.7 Bronchiolitis

Classically caused by RSV, common in autumn and winter (similar picture can be caused by influenza, parainfluenza and adenovirus infections). Very common; >80% children under 4 years possess neutralizing antibodies (although not very effective, hence repeated infections). Causes a range of symptoms from upper respiratory tract infections in older children and adults to bronchiolitis in the first 2 years of life. It is the most common cause of pneumonia in the first year.

## Presentation

- Respiratory distress and coryza
- Fever
- Hyperinflation

- Apnoea in very young infants
- Crackles widespread throughout lung fields  $\pm$  wheeze

## Diagnosis

- Immunofluorescence on nasopharyngeal aspirate

## Management

- Largely supportive
- Adequate hydration
- Humidified O<sub>2</sub> as required
- Evidence for use of bronchodilators (e.g. ipratropium bromide or salbutamol) not strong, but used frequently, often with apparent success

## Groups at risk of severe disease

- Bronchopulmonary dysplasia or other chronic lung disease, e.g. CF
- Congenital heart disease (especially cyanotic or associated with pulmonary congestion/hypertension)
- Immunocompromised children
- Disease in these children may lead to respiratory failure and requirement for ventilation

## Immunization

No active vaccine is currently available, and early studies with attenuated virus have led to increased severity in the subsequent infective episode. Anti-RSV immunoglobulin was useful in early studies in high-risk cases, but there were problems obtaining sufficient quantities and the usual concerns re blood products.

Humanized monoclonal anti-RSV antibody (palivizumab, Synagis) has been available in Europe since 1999 (1 year earlier in the USA).

- Given as monthly intramuscular injections during the RSV season
- Shown in trials of babies with bronchopulmonary dysplasia to reduce admissions, but no effect on the severe end of the disease (paediatric intensive care, mortality)
- Recommendations for use vary (commonly chronically O<sub>2</sub> dependent in first 2 years of life)

## 7.8 Viral pneumonia/Pneumonitis

### Common viruses

Viral respiratory illnesses are usually caused by *influenza*, *parainfluenza*, *human metapneumovirus*,

*adenovirus*, *RSV* or *coronavirus*. Signs and symptoms are indistinguishable from other pneumonias; treatment is supportive. Same groups of children as above are at high risk for severe illness.

## **Influenza**

Vaccine to seasonal flu is available and offered to those deemed to be most at risk. The vaccine contains subgroups of *influenza A* and *B*, including *influenza AH1N1*, following the pandemic in 2009. Neuraminidase inhibitors (e.g. oseltamivir) reduce spread of the virus in the airways if given within 48 hours of symptoms. Oral and inhaled preparations are available.

## **Recent viral epidemics**

*SARS (severe acute respiratory syndrome)* Caused by a *coronavirus* in 2003. Severe clinical picture in adults with high mortality, but children displayed only symptoms of mild upper respiratory tract infection (URTI) and recovered quickly.

### *Avian flu (H5N1)*

Caused by a strain of influenza A, this was first seen in 1997 but re-emerged in 2007. Unlike SARS, H5N1 caused severe disease in children with up to a 50% mortality rate. Limited person-to-person spread stopped this becoming pandemic.

### *Swine flu (H1N1)*

The WHO declared a pandemic in 2009 following the rapid spread of H1N1, a subtype of *influenza A*. It caused mortality in some previously healthy children, but most fatalities were in high-risk individuals and most healthy individuals had mild symptoms.

## **7.9 Tuberculosis and atypical mycobacterial infection**

See also [Chapter 15 – Section 5.1](#).

After a fall in incidence in tuberculosis (TB) worldwide over the last two to three decades following the development of successful anti-TB chemotherapy, there is now an increase in the number of cases, in both adults and children. This largely reflects the rapid increase in numbers infected with HIV, but is also being observed in areas of extreme poverty and overcrowding in countries such as the USA. A rise in cases of multidrug-resistant infection often results from poor adherence to treatment in index cases.

**Note that TB is a notifiable disease.**

This is a prime example of the ability of microorganisms either to exist within a host without causing adverse effects (TB infection) or to multiply, with or without tissue invasion and spread, and cause TB disease. Which one of these two situations evolves depends on both host (age, immune status, nutrition) and bacterial factors (numbers and virulence factors).

## **Pulmonary TB**



The major route of infection is via the respiratory tract (more rarely via the oral route leading to gut TB – must rule out immunodeficiency).

Once organisms have been inhaled they establish themselves in the periphery of the lungs, and elicit a host inflammatory response (largely via macrophages).

Spread to regional lymph nodes may also cause hilar adenopathy.

If inflammatory response is sufficient to keep the infection in check, the lesion may calcify and form a Ghon focus, which may be identified later on chest radiograph and be the only evidence of previous TB in an otherwise well person. This is much rarer in children than in adults, and most of the TB presenting in children is caused by the primary infection, resulting in the period from infection to disease often being as short as weeks.

## **Symptoms**

These vary and may be non-specific:

- Fever
- Irritability
- Weight loss and lethargy
- Cough
- Airway obstruction from lymphadenopathy; may lead to lobar collapse or less frequently to air trapping
- Dyspnoea and respiratory distress in severe cases especially if miliary
- Erythema nodosum

## **Radiology**

- Can vary greatly from isolated focus to hilar lymphadenopathy, lobar collapse/consolidation to miliary (seed-like) shadowing throughout lung fields
- Large caseating lesions not common in children

## **Extrapulmonary**

TB can infect most organs, in particular the brain, kidneys, gut and bone. Children are more prone than adults to extrapulmonary infection, the details of which are not discussed further here.

## **Diagnosis of TB**

High index of suspicion is important.

## **Tuberculin skin testing (TST)**

Intradermal administration of purified tuberculin protein will lead to a T-cell-mediated reaction in

sensitized individuals. Depending on the clinical situation, and whether bacillus Calmette–Guérin (BCG) has been administered, the size of the reaction considered to be significant may differ.

Significance of reaction size	
Size of reaction (mm)	Significant in:
>15	Any child
10–15	High risk – birth or arrival from high-risk country Contact with adults in high-risk group Young age
>5	Contact with an open known case (if no BCG) Clinical or radiographic evidence HIV infection

## Microbiology

- Sputum (rare in children)
- Gastric aspirates (morning)
- Bronchoalveolar lavage fluid
- Acid-fast bacilli may be visible on staining, otherwise culture requires up to 6–8 weeks

Some laboratories will test with polymerase chain reaction, although, because this is very sensitive, false positives can arise.

## Interferon-γ testing

These tests look for specific interferon-γ secreted by T cells exposed to *Mycobacterium tuberculosis*. They do not differ between latent and active TB and are usually performed alongside TST. There are two tests used in the UK: QuanterFERON Gold is carried out on whole blood and the T-SPOT TB test on T cells, making it more time-consuming but useful if child is immunosuppressed or on steroids.

## Treatment

Current guidelines state that all cases should receive quadruple therapy. Drug treatment is given in an initial phase of four drugs, followed by a maintenance phase of two drugs.

Usual first-line treatment	Potential side effects
Isoniazid (6 months)	Peripheral neuropathy Abnormal liver function tests

Rifampicin (6 months)	Orange urine/tears Hepatic enzyme induction (drug interactions) Abnormal liver function tests
Pyrazinamide (2 months)	Liver toxicity (only active against intracellular, actively dividing forms of the bacteria. Works best early in the treatment course. Good meningeal penetration if CNS disease)
Ethambutol (2 months)	Visual disturbance (Perform ophthalmic examination) Avoid in very young children

### **Additional therapeutic agents for high-risk/drug-resistant disease:**

- Ciprofloxacin
- Clofazimine
- Kanamycin
- Clarithromycin
- Streptomycin (intramuscular – rarely used in developed countries)

Children are rarely open cases (i.e. smear positive) and it is therefore unusual that they would be capable of transmitting the infection. After the first 2 weeks of treatment the child should be allowed to re-commence normal activities.

### **Neonatal contact**

A neonate born to a mother with active TB is at serious risk of acquiring the disease. If at the time the maternal diagnosis is realized (and treatment commenced) the infant has no signs of TB, the child should receive isoniazid prophylaxis, be closely followed up and receive a tuberculin test at 3 months. If negative, this should be repeated along with interferon- $\gamma$  test and, if all negative, prophylaxis stopped. If tuberculin test positive, assessment should be made for active TB. Thereafter, the guidelines for older children should be followed.

Contact tracing is a major public health issue. Cases of paediatric TB still arise in families where a parent is known to be infected but children have not been screened.

### **Pulmonary infection with atypical mycobacteria**

Examples include *Mycobacterium avium*, *M. intra-cellulare*, *M. kansasii* and *M. malmoense*. Unusual except in immunocompromised individuals or in children with CF. Symptoms range from those seen with TB infection to much milder presentation with fever or lethargy. In some cases, diagnosis may be suspected only after new changes are seen on a chest radiograph or, for example, in CF when the organisms are identified in the sputum. In CF, difficulties may arise in determining whether such organisms are pathogens. Treatment of a CF child is recommended if the child is unwell or if sputum is persistently positive.

## Treatment

Longer than for *M. tuberculosis* (up to 2 years). Choice of agents depends on organism and sensitivities. Usually a combination of the following is used:

- Rifampicin
- Clarithromycin/azithromycin
- Amikacin
- Ciprofloxacin
- Clofazimine
- Ethambutol

Notification and contact tracing are not required.

## 7.10 Infections in the immunocompromised host

### *Pneumocystis jiroveci* pneumonia (PCP)

Infection is caused by the fungus *Pneumocystis jiroveci*, formerly known as *Pneumocystis carinii* (hence PCP).

#### Presentation

Onset may be acute or insidious (especially in the older child), with tachypnoea, respiratory distress, fever,  $\pm$  cough, bilateral crackles and hypoxia; often normocapnic in early stages.

#### Chest radiograph

Classically bilateral interstitial and alveolar shadowing. May be normal, unilateral or focal.

#### Diagnosis

- Occasionally found on nasopharyngeal aspirate (NPA)
- Usually requires bronchoalveolar lavage (BAL)
- In rare cases, lung biopsy is required

#### Think

- Severe combined immune deficiency states (SCID)
- HIV (common in first year of life)
- DiGeorge syndrome
- (CD40 ligand deficiency; previously called hyper-IgM syndrome)

#### Treatment

- High-dose trimethoprim/sulfamethoxazole (pancytopenia, rash, fever)
- Pentamidine or dapsone used less frequently
- Steroids – role established in HIV; less certain otherwise
- If ventilated, consider surfactant
- Prophylaxis required after treatment and for any child at risk

## Other

Anti-*P. jiroveci* antibodies are common in healthy children.

## Cytomegalovirus

### Presentation

- Usually insidious – radiological appearance and likely immunodeficiencies similar to PCP
- May be congenital or acquired
- May coexist with extrapulmonary infection – ophthalmic examination required

### Diagnosis

- Antigen (DEAFF, detection of early antigen fluorescent foci) or polymerase chain reaction on NPA or BAL
- Detection in other body fluids, e.g. urine, does not confirm cytomegalovirus as the cause of pneumonitis

## Other

- Dual infection with *P. jiroveci* is not uncommon

## Other infections

Organisms causing a similar interstitial picture in immunocompromised patients include:

- Measles
- Varicella virus
- Herpes simplex virus
- Adenovirus
- Fungi
- Mycobacteria

## Lymphocytic interstitial pneumonitis

Although not related to any particular pathogen, this disorder is often confused with the opportunistic infections above, and is thus included here. It is seen in children with HIV or occasionally other immunodeficiency states, but is less common in adults:

- Tends to coexist with marked lymphadenopathy – parotid hyperplasia – and to decrease with falling CD4 count
- Presents either as chronic cough or hypoxia and clubbing if severe
- May be asymptomatic and detected radiologically only
- Treatment – nil if well; usually responds to steroids

## **When to suspect immune deficiency**

Normal children may have up to 10 upper respiratory tract infections per year. Suspect abnormal immune function if respiratory tract infections are:

- Unusually severe or prolonged
- Recurrent (although if same site, suspect anatomical abnormality or foreign body)
- Any case of pneumonitis/unexplained interstitial disease
- Associated with:
  - Infections in other sites, e.g. skin, liver, gastrointestinal tract, bone
  - Faltering growth
  - Persistent or generalized lymphadenopathy

## **8. INHALED FOREIGN BODY**

This will not be diagnosed unless thought about. There are major long-term implications if not removed, e.g. lobar collapse, bronchiectasis.

### **Suspect signs**

- Sudden-onset cough/wheeze/breathlessness
- May or may not give history of aspiration
- Ask about presence of older siblings in the case of an infant
- Unilateral signs: wheeze, absent or diminished air entry, tracheal/mediastinal deviation if severe

### **Chest radiograph**

- Either volume loss or hyperexpansion from air trapping on affected side
- Hyperexpansion best visualized on expiratory film

### **Management**

- Removal under rigid bronchoscopy (flexible bronchoscopy not recommended because removal is more difficult)
- Follow-up ventilation scan should be considered, especially in cases of non-inert foreign body, e.g. food. Peanuts are a particular problem because nut oil is very irritant and proinflammatory. If

removal is delayed, anti-inflammatory agents, e.g. steroids, may be useful to reduce airway narrowing

- Consider postoperative antibiotics, depending on findings
- Education is important, particularly the avoidance of peanuts in young children

## 9. PNEUMOTHORAX

In children this is usually associated with underlying disease.

- Gas trapping (e.g. severe asthma, CF)
- Bullae (e.g. Marfan syndrome)
- Other – Langerhans cell histiocytosis (in association with fibrotic, honeycomb changes on chest radiograph)
- Iatrogenic (high-pressure ventilation), traumatic and postoperative

### Symptoms and signs

- Dyspnoea, cough, chest pain
- Tracheal deviation, asymmetrical chest expansion and breath sounds
- Hyperresonance ± subcutaneous emphysema

### Management

- Depends on size on chest radiograph (all patients should have one)
- If small with minimal symptoms, can be managed conservatively and observed
- If larger with significant symptoms give O<sub>2</sub> (aids air absorption from pleural space) and drain. Aspiration may be sufficient, otherwise intercostal drain

### Recurrent

Consider pleurodesis:

- Surgical pleurectomy – more effective but more invasive
- Chemical adherence of pleura with either talc or doxycycline; painful
- May exclude possibility of future transplantation, e.g. in CF. Consider with care

Confused with:

- Neonatal cysts, diaphragmatic hernia, severe hyperinflation, e.g. inhaled foreign body

## 10. NEUROMUSCULAR DISORDERS

Can impair respiratory function at any of following sites: spinal cord, peripheral nerve, neuromuscular junction and muscle.

## 10.1 Spinal cord

### Spinal muscular atrophy

Disorder at levels of the anterior horn cells (atrophy). Autosomal recessive inheritance.

Presents as a floppy infant (Werdnig–Hoffman disease; with tongue fasciculation, preservation of eye muscles giving alert facial expression) or in less severe forms, as hypotonia and delayed motor milestones. Genetic tests are now available to aid diagnosis and classification.

Respiratory involvement always seen in types I and II (diaphragm spared), common in type III. Chest may be bell shaped. Lungs small.

Previously, severe forms would have been given a grave prognosis once diagnosed and allowed to die. More and more commonly, particularly in the USA, parents are demanding long-term ventilation. There are obvious ethical issues regarding this because there is currently no realistic chance of improvement or cure.

### Myelomeningocele

Rarely affects respiration unless very high.

### Cervical cord injury

Respiratory involvement depends on level.

## 10.2 Peripheral nerve

### Guillain–Barré syndrome

- Post-viral inflammatory ascending polyneuropathy
- Respiratory involvement common and most serious manifestation (intercostals and diaphragm):
  - This will be underestimated, unless specifically monitored
  - Do not assess with peak flow (this may be normal despite respiratory muscle compromise) – use vital capacity
- Bulbar involvement may lead to aspiration. Protective intubation may be required
- Good prognosis, even in severe cases requiring mechanical ventilatory support. Usual course:
  - Evolution 2–4 weeks
  - Plateau variable
  - Resolution 2–4 weeks later



- Specific treatments:
  - Intravenous immunoglobulin
  - Plasmapheresis in some cases

## 10.3 Neuromuscular junction

### Myasthenia gravis

- Autoimmune disease with antibodies directed against the acetylcholine (ACh) receptor
- Episodic muscle weakness, often mild, e.g. ptosis
- Weakness increases with exertion
- Management strategies include a trial of anticholinesterase drugs such as pyridostigmine, thymectomy or immunosuppressive treatments

Congenital myasthenia gravis is an autosomal recessive, non-autoimmune disease in which ACh synthesis or mobilization is defective. May respond to anticholinesterase drugs, but, if not, severe cases require long-term ventilatory support (see below) and assistance with feeding.

Neonatal myasthenia gravis is seen in up to 15% of babies born to affected mothers and results from transplacental passage of autoantibodies. Is transient, but affected infants may have feeding difficulties or require respiratory support. Treated with anticholinesterase drugs/exchange transfusion or plasmapheresis occasionally required.

### Botulism

- Rare
- Toxins produced by *Clostridium botulinum* (usually food borne, especially honey, which should be avoided in infants under the age of 1) lead to impaired release of ACh at neuromuscular junction. Bulbar muscles involved early, with respiratory failure in most cases. Good prognosis with adequate support. Botulinum toxin is currently being used as treatment for certain diseases with muscular spasm as major component

### Tick paralysis

- Very rare

## 10.4 Muscle

### Myotonic dystrophy

- Floppy infant in severe form
- Diaphragm involvement (eventration)

- Feeding problems  $\pm$  aspiration
- Maternal (when congenital) myotonia (muscles slow to relax, e.g. hand shake)
- Later problems – learning difficulties, cardiac conduction defects, baldness
- Triplet-repeat disease (others are Huntington disease, fragile X syndrome, Friedreich ataxia) with increasing severity in subsequent generations (genetic anticipation)

## Duchenne muscular dystrophy

- X-linked
- Weakness usually noted towards end of first decade.
- Oral glucocorticoid steroids prolong ambulatory phase and delay respiratory failure:
  - Death is usually from respiratory failure
  - Preceded by recurrent lower respiratory tract infections  $\pm$  aspiration from swallowing incoordination
- Regular overnight sleep studies should be performed to identify nocturnal hypoventilation once FVC  $<50\%$  or symptomatic
- Nocturnal non-invasive ventilation (NIV) corrects sleep hypoventilation and prolongs average survival to mid 20s and can prolong life to the fourth decade.

## Myopathies

- Respiratory involvement variable depending on type
- **Symptoms** include:
  - Respiratory infections
  - Morning headaches ( $\text{CO}_2$  retention)
  - Daytime drowsiness
- Management
  - Always consider possibility of respiratory involvement
  - Lung function testing
  - Polysomnography (overnight  $\text{O}_2$ ,  $\text{CO}_2$ , nasal airflow, chest wall movement, heart rate, respiratory rate  $\pm$  EEG, pH probe)
  - Non-invasive ventilation increasingly used (see below). Use once evidence of respiratory failure

## 10.5 Respiratory failure

Inability to maintain adequate gas exchange without additional support. If chronic, pulmonary hypertension and cor pulmonale may occur. Assess severity of respiratory effort (beware, if poor exhaustion is a late and worrying sign), vital signs, evidence of cor pulmonale, oxygen saturation and blood gases. Respiratory failure may manifest with hypoxia alone or hypercapnia as well. If the latter, supplementary oxygen is not an appropriate treatment; child will need non-invasive support (see below) or intubation.

## 10.6 Non-invasive ventilatory support

Acute respiratory failure requiring invasive ventilation in the intensive treatment unit setting will not be dealt with in this chapter, although the systems below can also be administered long term with the aid of a tracheostomy tube in cases where this is necessary.

Children with the neuromuscular disorders above (plus those with malacic airways and very occasionally those with chronic lung disease) may have chronic respiratory compromise and benefit from long-term ventilatory support.

This can be administered as either positive or negative pressure.

### Positive pressure

Both continuous (CPAP) and bilevel (bi-PAP) positive airway pressure can be administered through either a nose- or a facemask.

Both systems can be used at home with or without oxygen depending on the pathology. The devices are in general well tolerated, the only major problem being one of pressure sores caused by the tight-fitting mask.

### Negative pressure

Devices, including the cuirass jacket, have also been used in these settings. The jacket is worn around the chest, with closely fitted seals at either end. Negative pressure applied to the jacket causes inspiration. Expiration can be passive or assisted.

The benefits of this approach include a more physiological respiratory cycle. However, movement of the child is limited by the devices, which can also be very noisy.

In the UK, negative pressure is used much less frequently than positive. It is important to remember that significant weakness of the bulbar muscles, especially with any airway malacia, can lead to airway collapse and obstruction during applied negative pressure, which can lead to failure of the device.

## 11. RARE DISORDERS

### 11.1 Congenital disorders

#### Congenital thoracic malformations (CTMs)

##### Cystic adenomatoid malformation (CCAM)

- Type 1 – single or multiple large cysts (despite shift effects, usually good postoperative prognosis)

- Type 2 – multiple small cysts
- Type 3 – solid mass (poor prognosis)

## **Lobar sequestration**

- Mass of non-functional lung; abnormal communication with airway and usually supplied by systemic circulation
- Intra- or extralobar (often associated with other congenital abnormalities and polyhydramnios): may have derived from accessory lung bud, although exact aetiology is uncertain. Lower lobes most commonly affected, more often the left

## **Bronchogenic and duplication cysts**

- Remnant of primitive foregut derived from abnormal tracheobronchial budding
- Form up to 10% of mediastinal masses in children
- Contain normal tracheal tissue, filled with clear fluid
- May exist in various sites including paraoesophageal, with symptoms varying accordingly

CTMs may be diagnosed antenatally or postnatally but exact diagnosis can be made only on histological examination after resection. They cannot therefore be considered separately with regard to management.

Such lesions may be symptomatic:

- Recurrent infections, stridor, lobar collapse, dysphagia from oesophageal compression or haemorrhage
- In these cases surgical resection or embolization of the feeding vessel is advised
- Imaging with angiography to identify anatomy and blood supply is required before any surgery

Management of asymptomatic lesions is controversial:

- Most believe that resection of the lesion is advisable in order to prevent infections, malignant change (a very small risk that is not necessarily averted by complete resection) or other rare complications (haemorrhage, pneumothorax or air embolism)
- Some believe that asymptomatic lesions should be managed conservatively and the child followed up

## **Congenital lobar emphysema**

Over-inflation of the lobe as a result of an intrinsic deficiency of bronchial cartilage  $\pm$  elastic tissue.

### **The most common sites**

- Left upper lobe, right middle and upper lobes. Rare in lower lobes

## **Presentation**

- May be asymptomatic; detected on chest radiograph
- Neonatal respiratory distress
- Chest asymmetry, hyperresonance

## **Chest radiograph**

- Hyperlucent region; may be associated compression of other lobes
- Ventilation–perfusion scan may show absence of ventilation–perfusion in more severe cases

## **Management**

- Lobectomy of affected lobe if respiratory distress
- Mild respiratory distress/asymptomatic children can be managed conservatively because the emphysematous lobe does not become infected later on and does not affect lung growth
- Cardiac work-up: 1:6 have associated cardiac abnormality

## **Scimitar syndrome**

- Hypoplastic right lung with anomalous venous drainage (usually to inferior vena cava or right atrium)  $\pm$  systemic collateral arterial supply. ‘Scimitar’ sign is the vertical line caused by the right upper lobe pulmonary vein running into the inferior vena cava
- May be asymptomatic or lead to recurrent infection
- Right lung usually functions well and surgical correction of the vascular abnormalities is usually recommended

## **Diaphragmatic hernia**

- Incidence estimated at around 1 per 2500–3500 births. More common on the left. Main problems arise from the associated pulmonary hypoplasia, on both the affected side and the contralateral side when there is significant mediastinal shift. Diagnosis may be made antenatally on ultrasound
- Postnatal presentation includes respiratory distress, scaphoid abdomen and vomiting. Chest radiograph shows bowel loops inside thorax which may be confused with either cystic malformation or pneumothorax (use nasogastric tube both to confirm the diagnosis and to deflate the stomach, reducing the chance of rupture)
- Often associated with other malformations, in which case prognosis is worse

## **Treatment**

- Surgery required
- No clear evidence, but some suggestion that high-frequency oscillatory ventilation may help
- Pulmonary hypertension is quite common. May respond to nitric oxide or vasodilators
- Extracorporeal membrane oxygenation (ECMO)

## **Prognosis**

- With optimal management, including ECMO, mortality rate has decreased from about 50–60% to

20–40% in recent years

- Survivors may have problems associated with underlying pulmonary hypoplasia

## **$\alpha_1$ -Antitrypsin deficiency**

- Recessively inherited disorder
- Absence of liver-derived antiprotease leads to proteolytic destruction of pulmonary tissue and emphysema on exposure to oxidants, e.g. cigarette smoke and pollutants
- Rare for pulmonary problems to arise in children who are more likely to have the associated liver disease (eventual cirrhosis)
- PiMM refers to the homozygous normal state, PiZZ is homozygous deficient, PiSZ also causing disease

## **Alveolar proteinosis**

- Aetiology is uncertain, although some cases presenting as neonates are now known to be the result of deficiency of surfactant-associated protein B and others are linked to granulocyte–macrophage colony-stimulating factor (gm-csf). Lipid-laden type II pneumocytes desquamate into the alveolar spaces, leading to increasing hypoxia and respiratory distress
- **Chest radiograph** – resembles interstitial lung disease with widespread confluent airspace shadowing
- **Diagnosis** – made on lung biopsy
- **Prognosis** – poor
- In older child, whole lung lavages may help, but, in infants, the disease is almost universally fatal. Genetic counselling required

## **Congenital pulmonary lymphangiectasia**

- Rare dilatation of pulmonary lymphatics leading to severe neonatal respiratory distress and often pleural effusions
- Associated with congenital cardiac disorders such as obstructed venous drainage
- Prognosis very poor
- No specific treatment

## **11.2 Acquired disorders**

### **Obliterative bronchiolitis**

- Results from viral infection (usually adenovirus (50%) or mycoplasma (10–30%) but occasionally measles or RSV) or can follow lung or bone marrow transplantation
- Severe, widespread, small airway obstruction
- Dyspnoea, wheeze and hypoxia with eventual pulmonary hypertension
- Chest radiograph – hyperinflated lungs with patchy pruning of vascular markings

- CT – patchy areas of air trapping (honeycomb) and poor perfusion

In the early stages there may be some response to bronchodilators or steroids, but often no treatment is successful. If unilateral, may go on to Swyer–James (also called Macleod) syndrome of unilateral hyperlucent lung with diminished vascularity.

## Haemosiderosis

- Repeated episodes of pulmonary haemorrhage lead to accumulation of haemosiderin at the alveolar level
- Haemorrhage may be symptomatic with haemoptysis, or unrecognized, presenting with anaemia
- Aetiology is uncertain, although a subgroup of cases is associated with cows' milk protein allergy and positive antibodies, and responds to dietary manipulation
- Another subgroup have Goodpasture syndrome (positive anti-glomerular basement membrane antibodies)
- Similar clinical picture may occur with mitral stenosis or connective tissue diseases
- **Symptoms** – usually episodic: fever, dyspnoea, wheeze  $\pm$  haemoptysis
- **Chest radiograph** – may be normal but more commonly patchy shadowing
- **Diagnosis** – haemosiderin-laden macrophages in BAL
- **Management** – difficult:
  - Acute – treat hypoxia, anaemia
  - Longer term – steroids, hydroxychloroquine or alternative immunosuppressive drugs

## Sarcoid

- Extremely rare in childhood
- Multisystem granulomatous disease; may be confused with TB and chronic granulomatous disease
- **Symptoms**
  - Dry cough, dyspnoea
  - Clinical examination often unremarkable in early stages (may lead to clubbing later)
- **Chest radiograph**
  - Hilar lymphadenopathy
  - Patchy lung infiltrates
  - May be associated with extrapulmonary disease (skin, eye, kidney, gut)
- **Diagnosis**
  - Usually made on biopsy (Kveim test no longer performed)
- **Treatment**
  - May be self-limiting
  - Steroids  $\pm$  hydroxychloroquine if treatment required

## Interstitial lung diseases of childhood (ILDs)

This is a rare and diverse group of conditions leading to damage of the alveolar units and subsequent failure of adequate gas exchange. In some children an underlying cause is found. In others, there is no

apparent underlying cause and this group can be further subdivided by either histology or clinical presentation:

- 50% present in infancy
- Often gradual-onset dry cough, tachypnoea, dyspnoea, wheeze, hypoxia, clubbing. Older children describe chest pain and reduced exercise tolerance
- Widespread crackles throughout both lung fields usual, but chest can be clear. Signs of airway obstruction (barrel chest, apparent hepatomegaly)
- Chest radiograph/CT – ground-glass appearance, diffuse abnormality
- Differential diagnosis includes pneumonitis from opportunistic pathogens, e.g. PCP, extrinsic allergic alveolitis. Definitive diagnosis will require an open lung biopsy
- Histological findings vary from inflammation (more likely to respond to steroids) through to severe fibrosis (steroids less likely to succeed; antifibrotics, e.g. hydroxychloroquine, may be used)
- **Prognosis** – highly variable, ranging from subacute respiratory failure to a plateau phase with intermittent symptoms, or even recovery in some patients

## Pulmonary hypertension

Pulmonary hypertension may be primary (rare) or more commonly occurs secondary to another disease, including:

- Secondary to chronic hypoxia (chronic lung disease, ILD, obstructive sleep apnoea, severe CF):
  - Chronic hypoxia leads to pulmonary vasoconstriction and arterial wall change.
  - If treated early changes are reversible. If not treated, structural changes occur that are permanent and progressive
- Left-to-right shunts (high pulmonary arterial blood flow)
- Left heart disease (e.g. left-sided valvular, atrial or ventricular disease):
  - Multisystemic disorders such as HIV, sarcoidosis, connective tissue

Primary pulmonary hypertension presents with hypoxia, dyspnoea and, if severe, right heart failure. May present in the neonatal period as persistent fetal circulation (see [Section 1.3](#)). Secondary pulmonary hypertension should be suspected with increasing shortness of breath, increased oxygen requirement, syncopal episodes or unexpected deterioration not explained by the underlying diagnosis.

May respond to pulmonary vasodilators:

- High O<sub>2</sub>
- Nitric oxide (in ventilated children)
- Sildenafil
- Prostacyclin
- Nifedipine

Prognosis is improving with a 75–80% 3-year survival rate.



## 12. FURTHER READING

Beachey W (2007). *Respiratory Care Anatomy and Physiology: Foundations for clinical practice*, 2nd edn. London; Mosby.

Chernick V, Boat TF, Wilmott RW, Bush A, eds (2006). *Kendig's Disorders of the Respiratory Tract in Children*, 7th edn. London; WB Saunders.

Gibson RL, Burns JL, Ramsey BW (2003). Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* **168**;918–51.

Hull J, Forton J, Thomson A (2008). *Oxford Specialist Handbooks in Paediatrics: Paediatric respiratory medicine*. Oxford; Oxford University Press.

## **CONTENTS**

### **1. Juvenile idiopathic arthritis**

- [1.1 Systemic onset disease](#)
- [1.2 Polyarticular – rheumatoid factor negative](#)
- [1.3 Polyarticular – rheumatoid factor positive](#)
- [1.4 Oligoarticular \(persistent and extended\)](#)
- [1.5 Enthesitis-related arthritis](#)
- [1.6 Juvenile psoriatic arthritis](#)
- [1.7 Unclassified](#)

### **2. Other forms of childhood autoimmune arthritis**

- [2.1 Inflammatory bowel disease-related arthritis](#)
- [2.2 Juvenile sarcoidosis](#)
- [2.3 Reactive arthritis, including Reiter syndrome](#)
- [2.4 Rheumatic fever](#)
- [2.5 Infectious arthritis](#)
- [2.6 Notes on management of arthritis](#)

### **3. Connective tissue disorders of childhood**

- [3.1 Dermatomyositis](#)
- [3.2 Systemic lupus erythematosus](#)
- [3.3 Neonatal lupus](#)
- [3.4 Behçet syndrome](#)
- [3.5 Sjögren syndrome](#)
- [3.6 Scleroderma](#)
- [3.7 Overlap syndrome including mixed connective tissue disease](#)

### **4. Childhood vasculitis**

[4.1 Henoch–Schönlein purpura](#)

[4.2 Kawasaki disease \(mucocutaneous lymph node syndrome\)](#)

[4.3 Polyarteritis nodosa](#)

[4.4 Takayasu disease \(giant cell arteritis\)](#)

[4.5 Vasculitis with granuloma](#)

[4.6 Differential diagnosis of childhood rheumatic disorders](#)

## **[5. Miscellaneous disorders](#)**

[5.1 Osteogenesis imperfecta](#)

[5.2 Osteopetrosis](#)

[5.3 Osteoporosis](#)

[5.4 Hemihypertrophy](#)

[5.5 Hypermobility](#)

[5.6 Toe walking](#)

[5.7 Foot drop](#)

[5.8 Reflex sympathetic dystrophy](#)

[5.9 Non-accidental injury](#)

[5.10 Back pain](#)

[5.11 Torticollis](#)

## **[6. Further reading](#)**

---

# Rheumatology

---

## 1. JUVENILE IDIOPATHIC ARTHRITIS

This is the classification for autoimmune arthritis in childhood replacing ‘juvenile chronic/rheumatoid arthritis’ and Still disease.

Definition – a chronic arthritis that persists for a minimum of 6 consecutive weeks in one or more joints, starting before the age of 16 years and after active exclusion of other causes.

Epidemiology – 1 per 1000 children under 16 years of age.

### Classification

- By mode of onset during the first 6 months
- Eight groups:
  - Systemic onset
  - Polyarticular rheumatoid factor negative
  - Polyarticular rheumatoid factor positive
  - Oligoarticular – persistent
  - Oligoarticular – extended
  - Enthesitis-related arthritis (enthesitis = point of bony insertion of tendon)
  - Psoriatic
  - Unclassified

### Systemic disease

- High remittent fever and rash with one or more of the following: hepatomegaly, splenomegaly, generalized lymphadenopathy or serositis
- Arthritis may be absent at the onset, but myalgia or arthralgia is usually present

### Polyarticular onset

- Five or more joints develop in the onset period, usually somewhat insidiously and symmetrically
- May be further divided by the presence of immunoglobulin M (IgM) rheumatoid factor (also cyclic

citrullinated peptide positive in some)

## **Oligoarticular onset**

- The most common mode with four or fewer joints involved, particularly knees and ankles; once a joint is affected, it always counts even if does not recur
- Three clear subgroups have emerged, notably young children with positive anti-nuclear antibodies (ANAs) who are at risk from chronic iridocyclitis, older boys (aged 9 upwards) who frequently carry the histocompatible leukocyte antigen (HLA)-B27 and develop enthesitis (now classified as enthesitis-related arthritis), and those who extend past four joints (extended oligoarticular juvenile idiopathic arthritis) after 6 months
- Others presenting in this way include juvenile psoriatic arthritis, the arthritis of inflammatory bowel disease and Reiter syndrome, although some are as yet unclassified

## **1.1 Systemic onset disease**

### **General characteristics**

- Usually begins before 5 years of age but can occur throughout childhood into adult life
- Equal in boys and girls aged <5 years but female predominance in those aged >5 years

### **Clinical features**

- High once-daily fever spikes for >2 weeks
- Myalgia
- Arthralgia
- Malaise
- Rash – salmon-pink or red maculopapular eruption
- Lymphadenopathy – cervical, epitrochlear, axillary and inguinal
- Hepatosplenomegaly
- Serositis – 40% mainly pericarditis
- Hepatitis
- Progressive anaemia
- Macrophage activation syndrome
- Arthritis – knees, wrists and carpi, ankles and tarsi, neck, followed by other joints

### **Investigations**

- Erythrocyte sedimentation rate (ESR) – high
- Haemoglobin – low (normochromic/normocytic)
- White blood cell count – raised (neutrophil leukocytosis)
- Platelets – raised ( $>400 \times 10^6/l$ )
- IgM rheumatoid factor – negative

- ANAs – negative

## Course and prognosis

- Half will have recurrent episodes of systemic disease
- Progressive arthritis occurs in about a third, irrespective of whether there are systemic exacerbations
- The younger the age of onset, the greater the risk of poor growth, both somatic and of joints
- Amyloidosis occurs in some children with persistent disease activity, predominantly among Europeans

## Management

- Physiotherapy to maintain joint mobility and muscle function
- Non-steroidal anti-inflammatory drugs (NSAIDs) to control pain, inflammation and fever
- Corticosteroids in severe disease, either as pulsed, intravenous, single daily dose or given on alternate days
- Methotrexate especially for arthritis
- Ciclosporin or IVIg (intravenous immunoglobulin) for systemic features
- Etanercept (tumour necrosis factor [TNF] receptor – NICE approved for 4–17 year olds) or infliximab/adalimumab (anti-TNF receptor antibody) for disease that is resistant to other medical management or for patients in whom there is significant drug toxicity – very little is known of long-term toxicity; use in specialist centres only
- Anti-interleukin-1 (anti-IL-1; anakinra) effective when other treatments failed or side effects
- Anti-IL-6 – tocilizumab very successful in patients failing above treatments

## 1.2 Polyarticular – rheumatoid factor negative

### General characteristics

- Any age, occasionally before the first birthday
- Female predominance

### Clinical features

- Polyarthritis can affect any joint; the most commonly affected are the knees, wrists, ankles, and proximal and distal interphalangeal joints of the hands; metacarpophalangeal joints are often spared
- Limitation of neck and temporomandibular joint movement is common
- Flexor tenosynovitis
- Low-grade fever, occasionally
- Mild lymphadenopathy and hepatosplenomegaly, occasionally

## Investigations

- ESR – elevated
- Haemoglobin – may be reduced
- White blood count – mild neutrophil leukocytosis
- Platelets – moderate thrombocytosis
- IgM rheumatoid factor – negative
- ANAs – occasionally positive

## Course and prognosis

- Variable
- May be monocyclic but prolonged over several years with good functional outcome
- Recurrent episodes tend to cause progressive deformities

## Management

- Physiotherapy to maintain and improve joint and muscle function
- Splinting to prevent deformity
- NSAIDs to control pain and inflammation
- Methotrexate is very effective and can be used early on to prevent deformity
- Anti-TNF treatment if other disease-modifying anti-rheumatic drugs (DMARDs) have failed

## 1.3 Polyarticular – rheumatoid factor positive

### General characteristics

- Aged >8 years at onset
- Female predominance

### Clinical features

- Polyarthritis affecting any joint, but particularly the small joints of the wrists, hands, ankles and feet; knees and hips often early, with elbows and other joints later
- Rheumatoid nodules on pressure points, particularly elbows. Vasculitis uncommon and often late, nailfold lesions, ulceration

## Investigations

- ESR – usually elevated
- Haemoglobin – moderate anaemia
- IgM rheumatoid factor – persistently positive and in high titre
- Anti-cyclic citrullinated peptide (CCP) may be positive and predictive of prognosis

- ANAs – may be positive
- HLA-DR4 – frequently present
- Radiographically – early erosive changes of affected joints, particularly of hands and feet

## **Course and prognosis**

- Persistent activity with serious joint destruction and poor functional outcome
- Additional long-term hazards include atlantoaxial subluxation, aortic incompetence and amyloidosis

## **Management**

- Physiotherapy to maintain and improve joint and muscle function
- Splinting to preserve function
- NSAIDs
- Slow-acting drugs early
- Methotrexate
- Anti-TNF treatment if other DMARDs failed
- Surgical intervention, such as replacement arthroplasties, often required later

## **1.4 Oligoarticular (persistent and extended)**

### **General characteristics**

- Under 6 years of age
- Female predominance

### **Clinical features**

- Arthritis affecting four or fewer joints: commonly knee, ankle, elbow or a single finger
- Early local growth anomalies
- Risk (2:3) of chronic iridocyclitis in the first 5 years of disease, ANA associated
- If four or fewer joints after 6 months then defined as persistent oligoarticular, if more than four joints are affected it is described as extended oligoarticular

### **Investigations**

- ESR – may be elevated or normal, initially
- Haemoglobin – normal
- White blood count – normal
- Platelets – normal
- IgM rheumatoid factor – negative
- ANAs – frequently positive



- HLA-A2, -DR5 and -DR8

## Course and prognosis

- Exacerbations and remissions
- Alteration in growth of affected limb
- Long-term prognosis of joints good, except for the one in five who develop polyarthritis (five or more joints) over a period of years (extended)
- Iridocyclitis is bilateral in two-thirds; the course is independent of the joints – its prognosis depends on early detection and good management

## Management

- Physiotherapy to maintain muscle and joint function
- NSAIDs help only symptoms not disease
- Local corticosteroid injection – triamcinolone hexacetonide is most effective
- Frequent ophthalmological assessment (3- to 6-monthly)
- Methotrexate for extended oligoarticular juvenile idiopathic arthritis
- Anti-TNF treatment in extended if methotrexate failed

## 1.5 Enthesitis-related arthritis

### General characteristics

- Age  $\geq 9$  years
- Male predominance

### Clinical features

- Peripheral arthritis predominantly affecting the joints of the lower limb
  - Enthesopathies – plantar fascia, Achilles tendon, patella tendon
  - Acute iritis
  - Sacroiliac pain in some
  - Axial disease in some
- } either of these can be the presenting feature

### Investigations

- ESR – normal to high
- Full blood count – usually normal
- IgM rheumatoid factor – negative
- HLA-B27 – present in 90%

## Course and prognosis

- Functional outcome is good in two-thirds of cases
- Some joint extension may occur
- Over time, one-third can develop serious hip problems, cervical and other spinal involvement, impaired temporomandibular function, as well as other features of spondylitis

## Management

- Physiotherapy, including hydrotherapy, to maintain mobility: particularly important if spinal involvement occurs
- NSAIDs
- Local corticosteroid injections; hip arthroplasty may be needed in a small proportion
- Sulfasalazine is the disease-modifying drug of choice; methotrexate is also effective
- Anti-TNF treatment if other DMARDs failed, especially for axial disease

## 1.6 Juvenile psoriatic arthritis

### General characteristics

- An arthritis associated, but not necessarily coincident, with a typical psoriatic rash, or arthritis, plus at least three of four minor criteria: dactylitis, nail pitting, psoriatic-like rash or family history of psoriasis
- Female predominance
- Family history of psoriasis (common) or arthritis (but less so)

### Clinical features

- Asymmetrical arthritis
- Flexor tenosynovitis
- Occasionally severe destructive disease
- Systemic features rare
- Nail pitting
- Onycholysis
- Psoriasis

### Investigations

- ESR – varies with number of joints, may be high
- Haemoglobin – may fall
- White blood count – may increase (neutrophils)
- IgM rheumatoid factor – negative
- ANAs – can be positive

## Course and prognosis

- Young onset can be associated with iridocyclitis
- Remitting–relapsing course, even into adult life
- Occasionally severely destructive
- Occasionally spondylitis (inflammation of spinal joints) develops

## Management

- Physiotherapy
- NSAIDs and steroid joint injections
- Methotrexate early for polyarticular presentation
- Anti-TNF treatment if other DMARDs failed

## 1.7 Unclassified

All those that do not meet the criteria for the above.

## 2. OTHER FORMS OF CHILDHOOD AUTOIMMUNE ARTHRITIS

### 2.1 Inflammatory bowel disease-related arthritis

#### General characteristics

- Arthritis associated with either ulcerative colitis or Crohn disease
- Over 4 years of age
- Male and female predominance equal

#### Clinical features

- Arthritis usually occurs after the onset of bowel symptoms, but occasionally begins coincident with, or even precedes, them
- Arthritis is usually oligoarticular: knees, ankles, wrists and elbows
- Two forms:
  - Benign peripheral arthritis coinciding with active bowel disease
  - In older patients, who belong to the spondylitic group, the joint activity does not necessarily link with bowel activity

#### Associated features

- Erythema nodosum
- Pyoderma gangrenosum

- Mucosal ulcers
- Fever
- Weight loss
- Growth retardation
- Acute iritis – in the spondylitic group

## Investigations

- Platelets – normal/elevated
- ESR – usually elevated
- Haemoglobin – usually low (normochromic, normocytic)
- White blood count – normal
- IgM rheumatoid factor – negative
- ANAs – negative
- HLA-B27 present in the spondylitic group

## Course and prognosis

- Peripheral arthropathy involves few joints and is episodic and benign
- Prognosis for joint function is excellent
- Prognosis for the spondylitic group is similar to that of ankylosing spondylitis

## Management

- Physiotherapy as appropriate
- Treatment of the underlying bowel disorder
- NSAIDs with care, because of gastrointestinal side effects (ibuprofen may be the drug of choice and use antacids such as ranitidine)
- Sulfasalazine or methotrexate may be helpful for both subgroups
- Infliximab (anti-TNF treatment) is effective

## Causes of erythema nodosum

- Idiopathic
- Streptococcal infection
- Tuberculosis
- Leptospirosis
- Histoplasmosis
- Epstein–Barr virus infection
- Herpes simplex virus infection
- *Yersinia* sp. infection
- Sulphonamides
- Oral contraceptive pill
- Systemic lupus erythematosus

- Crohn disease
- Ulcerative colitis
- Behçet syndrome
- Sarcoidosis
- Hodgkin disease

## 2.2 Juvenile sarcoidosis

- Can occur at any age
- Usually presents with painless swelling of joints and marked tenosynovitis
- Can have rash
- Panuveitis can be severe so regular eye checks must be performed
- With musculoskeletal disease lymphadenopathy is not seen; renal disease occurs in children
- Angiotensin-converting enzyme (ACE) is raised in at least 50% of children who are patients
- Treat with steroids and methotrexate or azathioprine

## 2.3 Reactive arthritis, including Reiter syndrome

Acute arthritis occurring after an intercurrent infection, without evidence of the causative organism in the joint. Any age, but particularly male teenagers.

### Clinical features

- Arthritis
  - Urethritis/balanitis/cystitis
  - Conjunctivitis
  - Mouth ulceration
  - Fever
  - Rashes, including keratoderma blennorrhagica (macules – pustular on palms, soles, toes, penis)
- } Typical triad for Reiter syndrome

If only two salient features occur, it is often referred to as ‘incomplete Reiter syndrome’.

### Investigations

- ESR – raised
- Haemoglobin – normal
- Mild neutrophil leukocytosis
- IgM rheumatoid factor – negative
- ANAs – negative
- Occasionally positive stool or urethral culture (*Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*, *Chlamydia* spp.)
- High incidence of HLA-B27

## Course and prognosis

- Usually self-limiting, but the arthritis can be severe and persistent
- Some may later develop ankylosing spondylitis

## Management

- Antibiotics initially, if an organism is found
- Physiotherapy to maintain function of joints and muscles
- NSAIDs
- Sulfasalazine if joint problems persist

## Conditions associated with HLA-B27 positivity

- Ankylosing spondylitis – 95% of patients
- Reiter syndrome
- Arthritis of inflammatory bowel disease and psoriasis
- Acute iridocyclitis
- Enthesitis-related arthritis of older children
- Reactive arthritis following infection with *Salmonella* and *Shigella* spp., *Yersinia enterocolitica*, *Campylobacter* sp.

## 2.4 Rheumatic fever

### General characteristics

- An inflammatory reaction in joints, skin, heart and central nervous system (CNS) following a group A haemolytic streptococcal infection
- Age generally >3 years
- Occurs in both sexes, but in girls more often than boys

### Revised Jones criteria

#### Major manifestations

Carditis (severe pancarditis can occur in first or subsequent attacks)  
Polyarthritis (flitting)  
Subcutaneous nodules  
Chorea  
Erythema marginatum

#### Minor manifestations

Fever  
Arthralgia

Previous rheumatic fever and rheumatic heart disease

Raised acute phase (ESR, C-reactive protein)

Prolonged P–R interval on ECG

Plus supporting evidence of a preceding streptococcal infection.

Throat swab positive for group A streptococcus, increased anti-streptolysin O and anti-DNAse B titres.

## Investigations

- ESR – raised if not in cardiac failure
- Haemoglobin – may fall with chronic disease
- White blood count – normal or slight rise
- IgM rheumatoid factor – negative
- ANAs – negative
- ECG – may be abnormal, prolonged P–R
- Echocardiogram – may show valvular or myocardial dysfunction

## Course and prognosis

- Average attack lasts 6 weeks
- High risk of recurrence in patients who do not receive adequate prophylaxis against streptococcal infection

## Management

- Bed rest in the acute phase
- Penicillin to eradicate residual streptococcal infection
- Salicylate therapy
- Corticosteroids in patients with significant carditis
- Prophylactic oral or intramuscular penicillin after an attack required into adult life

## 2.5 Infectious arthritis

### Viral

- Adenovirus, parvovirus, cytomegalovirus, rubella virus, mumps virus, varicella virus

### Lyme disease

- *Borrelia burgdorferi*

### Bacterial

- *Haemophilus* sp. (young), staphylococci, streptococci, meningococci, gonococci
- Mycobacteria – both typical and atypical

## Fungal

- Blastomycosis, coccidioidomycosis, cryptococci
- *Histoplasma capsulatum*

## Other

- *Mycoplasma* spp.
- Guinea worm

## Differential diagnosis of childhood arthritis

- Infections
- Post-infectious arthritides
- Mechanical, including hypermobility
- Juvenile idiopathic arthritis
- Neoplasm including acute lymphoblastic leukaemia
- Other autoimmune/vasculitic diseases
- Rheumatic fever

## 2.6 Notes on management of arthritis

### Physiotherapy, occupational therapy, podiatry, splinting

Arthritis causes contractures and physiotherapy, occupational therapy, podiatry and splinting are used to overcome this. The physiotherapist teaches active and passive joint movements aiming to maximize function and avoid contractures. Hydrotherapy is used in early disease. Splinting at night is used to prevent or help correct fixed flexion deformities. The podiatrist has a specific interest in foot care. The occupational therapist's role is to maximize the child's functioning within as normal an environment as possible using aids/adaptations as needed.

### Orthoses

- Orthoses are useful in helping to prevent contractures, maintaining a good position if contractures have been repaired and providing joint stability
- They are particularly useful for helping individual children with mobility
- The type of orthoses depends on the child's individual needs

For example, they may be ankle-foot orthoses if there is just ankle and foot involvement, extending to the knee if the knee is involved. Should there be a scoliosis, thoracolumbar orthoses are available.



## Side effects of commonly used drugs

- NSAIDs – gastrointestinal (may need ranitidine, omeprazole), neurological (headaches, mood)
- Steroids – bone (use calcium, vitamin D), growth, cataract, weight gain
- Methotrexate – nausea (may need ondansetron) liver and bone marrow toxicity (requires monitoring of blood count and liver function)
- Anti-TNF treatment – hypersensitivity reactions, infections, particularly tuberculosis, headaches

## Antinuclear antibodies

- Not diagnostic or specific for any particular disease
- React with various nuclear constituents

## Causes of ANA positivity in children

- Systemic lupus erythematosus
- Juvenile idiopathic arthritis
- Chronic active hepatitis
- Scleroderma
- Mixed connective tissue disease
- Drugs, e.g. anticonvulsants, procainamide
- Epstein–Barr virus infection

## 3. CONNECTIVE TISSUE DISORDERS OF CHILDHOOD

### 3.1 Dermatomyositis

#### General characteristics

- Non-suppurative myositis with characteristic skin rash and vasculitis
- Occurs in girls more often than in boys
- Peak incidence at 4–10 years of age

#### Clinical features

- Muscle pain and occasional tenderness
- Muscle weakness – limb, girdle, neck, palate, swallowing
- Oedema
- Skin rash – periorbital heliotrope eruption and oedema
- Deep red patches over extensor surface of finger joints (Gottron patches), elbows, knees and ankle joints
- Vasculitis and skin ulceration
- Nailfold and eyelid – dilated capillaries

- Retinitis in some
- Myocarditis with arrhythmias can occur
- Arthralgia/arthritis with contractures
- Limited joint mobility
- Gastrointestinal dysfunction
- Pulmonary involvement
- Calcinosis (after 1–2 years)

## Investigations

- Magnetic resonance imaging (MRI) of muscles shows inflammation in muscles and perifascicular areas
- ESR – usually normal
- Serum muscle enzymes (creatine kinase, lactate dehydrogenase) – elevated
- Electromyography (EMG) – shows denervation/myopathy
- Muscle biopsy shows inflammation and/or fibre necrosis and small-vessel occlusive vasculitis
- ANAs – positive in some

## Course and prognosis

- Variable
- Prognosis usually good with adequate treatment
- A small proportion can develop extensive muscle wasting, severe contractures and widespread calcinosis

## Management

- Gentle physiotherapy and splinting, followed by more active physiotherapy as muscle inflammation subsides
- Corticosteroids in sufficient dosage to restore function and normalize enzymes
- Cytotoxic drugs – methotrexate, azathioprine, ciclosporin, cyclophosphamide, if required
- Anti-TNF treatment
- Careful monitoring is essential, with particular attention to palate and respiratory function, as well as to possible gastrointestinal problems

## 3.2 Systemic lupus erythematosus

### General characteristics

- Onset usually after 5 years of age
- Before puberty, female:male incidence ratio 3:1; after puberty 10:1
- Higher incidence in black, Oriental, Asian, Native American and Latin American individuals
- Can be associated with complement deficiencies of C2 and C4

- Possible associations with HLA antigens HLA-B8, -DR2, and -DR3

## **Clinical features**

- General malaise
- Weight loss
- Arthralgia or arthritis
- Myalgia and/or myositis
- Fever
- Mucocutaneous lesions:
  - Malar rash
  - Papular, vesicular or purpuric lesions
  - Vasculitic skin lesions
  - Alopecia
  - Oral ulcers
  - Photosensitivity
- Renal disease common, even at onset
- Pulmonary – pleuritis, interstitial infiltrations
- Cardiac – pericarditis, myocarditis, Libman–Sacks endocarditis
- CNS involvement – seizures, headache, psychosis
- Cerebral dysfunction – blurred vision, chorea, transverse myelitis
- Gastrointestinal involvement – hepatosplenomegaly, mesenteric arteritis, inflammatory bowel disease
- Eye – retinitis, episcleritis, rarely, iritis
- Raynaud phenomenon, occasionally

## **Investigations**

- ESR – raised
- Haemoglobin – low: autoimmune haemolytic anaemia in some; anaemia of chronic disease
- Leukopenia – mainly lymphopenia
- Thrombocytopenia in some
- IgM rheumatoid factor – may be positive
- ANAs – strongly positive
- Antibodies to double-stranded (ds) DNA usually present in two-thirds
- Total haemolytic complement and its components low
- Anti-cardiolipin antibodies and lupus anticoagulant may be present

## **Course and prognosis**

- Highly variable
- Relates closely to the extent and severity of systemic involvement
- Potential causes of death include infectious complications, including bacterial endocarditis
- Other problems include myocardial infarction, pulmonary fibrosis and renal failure
- Meticulous monitoring essential

# Management

- Hydroxychloroquine for skin, joints, pulmonary involvement
- Corticosteroids for systemically ill patients
- Cytotoxic drugs for serious intractable disease
- Anti-platelet drugs for thrombotic episodes
- Rituximab for refractory renal, CNS and haematological disease

## Revised criteria for the classification of systemic lupus erythematosus

A person shall be said to have systemic lupus erythematosus (SLE) if any four or more of 11 criteria are present:

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis:  
Pleuritis  
OR  
Pericarditis
7. Renal disorder:  
Persistent proteinuria  
 $\leq 0.5\text{g/day}$   
OR  
Cellular casts
8. Neurological disorder  
Seizures disorder  
OR  
Psychosis
9. Haematological disorder:  
Haemolytic anaemia  
OR  
Leukopenia  
OR  
Lymphopenia  
OR  
Thrombocytopenia
10. Immunological  
(a) Anti-phospholipid antibodies  
OR  
(b) Anti-DNA: antibody to native DNA  
OR

(c) Anti-Sm: presence of antibody to Sm nuclear  
OR

(d) False-positive serological test for syphilis

11. Antinuclear antibody:

An abnormal titre of ANA

### 3.3 Neonatal lupus

#### General characteristics

- Present in neonatal period; acquired transplacentally
- Associated with maternal autoantibodies (particularly Ro/La) and with maternal lupus or Sjögren syndrome

#### Clinical features

- Rash – lesions of discoid lupus or subacute cutaneous lupus
- Congenital heart block – occasional endocardial fibroelastosis
- Thrombocytopenia
- Hepatic or pulmonary disease, haemolytic anaemia – uncommon

#### Investigations

- ANAs – particularly Ro/La
- Thrombocytopenia, anaemia, leukopenia
- Platelet antibodies – positive Coombs test
- ECG

#### Course and prognosis

- Cutaneous and haematological manifestations transient
- Congenital heart block permanent
- Hepatic fibrosis occasional
- Some risk of SLE in teenage or adult years

#### Management

- Symptomatic for transient manifestations
- Heart block may require pacemaker

### 3.4 Behçet syndrome

## **General characteristics**

- A clinical triad of recurrent oral aphthous ulcers, recurrent genital ulcers and uveitis
- Male predominance
- High incidence in Japan, the Mediterranean and the Middle East

## **Clinical features**

- Oral ulcers
- Genital ulcers
- Severe uveitis – may lead to glaucoma and blindness
- Arthritis
- Rash – skin hypersensitivity
- Bowel involvement
- Meningoencephalitis, brain-stem lesions and dementia

## **Treatment**

- Steroids, thalidomide, anti-TNF treatment are all effective

## **3.5 Sjögren syndrome**

### **General characteristics**

- Dry eyes (keratoconjunctivitis sicca)
- Dry mouth and carious teeth
- Parotitis
- May occur alone or in association with other rheumatic disease
- Occasional complication of renal disease or lymphoreticular malignancy

## **3.6 Scleroderma**

### **Localized (majority of paediatric cases)**

- Morphea: thickened shiny pale skin then darkens as resolves with loss of subcutaneous tissue
  - Single patch
  - Multiple patches
- Linear: thickened plaque which cause loss of subcutaneous tissues and contractures over joints and loss of bone growth
  - Face, forehead and scalp (en coup de sabre)
  - Limb (en bande)

## **Diffuse (systemic sclerosis/CREST [calcinosis cutis, Raynaud phenomenon, oesophageal hypomobility, sclerodactyly, telangiectasia])**

- Rare in childhood; develop tightening of skin of hands, feet and face; systemic problems include respiratory and gastrointestinal problems and renal disease

### **3.7 Overlap syndrome including mixed connective tissue disease**

#### **General characteristics**

- Overlapping features of juvenile idiopathic arthritis, SLE, systemic sclerosis and dermatomyositis
- Affects particularly older girls

#### **Clinical features**

- Arthritis
- Tenosynovitis – both flexor and extensor tendons of fingers, causing contractures
- Raynaud phenomenon – common
- Myositis
- Pleuropericardial involvement
- Dysphagia
- Parotid swelling

#### **Investigations**

- ESR – high
- Haemoglobin – often low
- White blood count – usually normal
- Platelets – can be low
- ANAs – positive
- Anti-RNP antibodies in high titres indicate the designation of mixed connective tissue disease
- Anti-DNA antibodies – negative or in low titre
- IgM rheumatoid factor – occasionally positive

#### **Course and prognosis**

- Slowly develops over years
- May evolve into other recognizable conditions, such as sclerodactyly and, later, other features of systemic sclerosis or SLE may appear

#### **Management**

- Mild disease is managed with NSAIDs and/or antimalarials

- More severe disease may require corticosteroids, with or without a cytotoxic agent
- Careful monitoring is required to detect signs of potentially serious systemic disease (e.g. nephritis)

## 4. CHILDHOOD VASCULITIS

Childhood vasculitis encompasses a wide range of clinical syndromes that are characterized by inflammatory changes in the blood vessels. The clinical expression of the disease and its severity depend on the type of pathological change, the site of involvement and the vessel size. The two most common forms seen in children are Henoch–Schönlein purpura and Kawasaki disease.

### 4.1 Henoch–Schönlein purpura

#### General characteristics

- Inflammation of small vessels, capillaries – pre- and postcapillary vessels
- May be precipitated by infection, particularly haemolytic streptococci
- Onset generally after the age of 3 years; there is a slight male predominance

#### Clinical features

- Petechiae
- Rash – urticarial lesions evolving into purpuric macules, usually on the legs, feet and buttocks
- Cutaneous nodules – particularly over the elbows and knees
- Localized areas of subcutaneous oedema that affect the forehead, spine, genitalia, hands and feet
- Arthritis – transient, involving large joints
- Gastrointestinal involvement – colicky abdominal pain and/or gastrointestinal bleeding
- Renal involvement – nephritis, occasionally nephrosis

#### Investigations

- ESR – normal or high
- Full blood count – normal
- Haematuria and/or proteinuria and/or casts
- IgA complexes in glomeruli and involved skin
- Serum IgA is often raised

#### Course and prognosis

- Episodes of Henoch–Schönlein purpura are self-limiting
- Recurrences occasionally occur
- Long-term morbidity related to renal involvement



# Management

- Supportive care
- Corticosteroids in severe disease

## 4.2 Kawasaki disease (mucocutaneous lymph node syndrome)

### General characteristics

- An acute febrile disease, first described in Japan after the 1940s
- Although now seen in all racial groups throughout the world, it appears to be more common in Oriental individuals
- Occurs in young children, even before the first birthday, and has a slight male predominance

### Investigations

- ESR – high
- Haemoglobin – lowered
- White blood count – raised
- Polymorph leukocytosis
- Platelets – raised
- ANAs – negative
- IgM rheumatoid factor – negative
- Echocardiography – arteriogram

### Diagnostic criteria

- Fever lasting 5 days or more
- Bilateral conjunctival injection
- Changes in lips and oral cavity
- Changes in extremities – reddening and oedema of palms and soles followed by desquamation
- Polymorphous erythematous rash
- Cervical lymphadenopathy

For diagnosis, a fever and four features are required.

### Clinical features

As in diagnostic criteria, plus:

- Irritability
- Pericarditis
- Valvular dysfunction

- Coronary artery disease
- Arthritis and/or arthralgia
- Gastrointestinal symptoms
- Urethritis
- Central nervous system problems – aseptic meningitis
- Iritis

## Course and prognosis

- Acute and convalescent stage lasts up to 10 weeks
- Coronary aneurysms or widening in some 20% of cases
- Death due to coronary vasculitis causing myocardial infarction or rupture of an aneurysm occurs in about 1% of cases

## Management

- Supportive care
- Careful observation to detect and manage complications
- Salicylate therapy
- Intravenous  $\gamma$ -globulin
- Steroids are used and anti-TNF (Infliximab)

## 4.3 Polyarteritis nodosa

### General characteristics

- A vasculitis affecting small- to medium-sized muscular arteries in either a generalized or a cutaneous form
- Age range 3–16 years with equal sex distribution

### Clinical features

- Fever
- Abdominal pain
- Arthralgia/myalgia
- Rash:
  - Petechial or purpuric in the generalized form
  - Tender subcutaneous nodules and livedo reticularis in the cutaneous form
- Hypertension
- Renal involvement
- Neurological disease

### Investigations

- ESR – high
- Haemoglobin – <10 g/l
- Leukocytosis
- Urinary abnormalities
- Anti-streptolysin O titre (ASOT) – elevated in some
- Histology – focal necrosis in small- and medium-sized arteries

## **Course and prognosis**

- Cutaneous form is usually benign but relapses may occur
- Prognosis is worse in the generalized form, depending on the organ involvement

## **Management**

- Steroids – high dose (2 mg/kg per day) in the generalized form
- Steroids and immunosuppressants for severe cases
- Penicillin prophylaxis, if streptococcal aetiology is proved

## **4.4 Takayasu disease (giant cell arteritis)**

### **General characteristics**

- A panarteritis of the aorta and its large branches leading to thrombosis, stenosis or occlusion
- Primarily affects young adult women, but may occur in children
- More common in Oriental and black individuals

### **Clinical features**

- Claudication – in the arms and also the legs, and absent pulses
- Myalgia
- Hypertension
- Malaise
- Fever

### **Investigations**

- ESR – high
- Haemoglobin – low
- White blood count – neutrophil leukocytosis
- Using a combination of Doppler ultrasound and angiography it is possible to show occlusion, stenosis or aneurysms

### **Course and prognosis**

- Variable

## **Management**

- Steroids with or without cytotoxic therapy
- Reconstructive surgery when the disease is inactive

## **4.5 Vasculitis with granuloma**

### **Churg–Strauss syndrome**

#### **General characteristics**

- A systemic necrotizing vasculitis of small arteries and veins, accompanying asthma and associated with eosinophilia

#### **Clinical features**

- Lung involvement – asthma, transient pulmonary infiltrates
- Rash – palpable purpuras and tender subcutaneous nodules
- Peripheral neuropathy
- Renal involvement – occasionally

### **Wegener granulomatosis**

#### **General characteristics**

- This also is a necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, accompanied by glomerulonephritis

#### **Clinical features**

- Pulmonary granulomas
- Destructive granulomas of the ears, nose and sinuses
- Rash
- Glomerulonephritis
- Eye lesions

#### **Special investigation**

- Anti-neutrophil cytosolic antibodies

## **Management**

- Combined therapy with steroids and cyclophosphamide

## 4.6 Differential diagnosis of childhood rheumatic disorders

- Infection
- Neoplasm
- Blood dyscrasias
- Mechanical anomalies, including injury
- Biochemical abnormalities
- Genetic and/or congenital anomalies
- Oddities do occur

## 5. MISCELLANEOUS DISORDERS

### 5.1 Osteogenesis imperfecta

Osteogenesis imperfecta is a disorder of connective tissue characterized by bone fragility. The disease encompasses a phenotypically and genetically heterogeneous group of inherited disorders that result from mutations in the genes that encode for type 1 collagen. The disorder is manifest in tissues in which the principal matrix is collagen, namely bone, sclerae and ligaments. The musculoskeletal manifestations vary from perinatal lethal forms, to moderate forms with deformity, and a propensity to fracture to clinically silent forms with subtle osteopenia and no deformity, as discussed below.

#### **Osteogenesis imperfecta type I**

This is characterized by osteoporosis and excessive bone fragility, distinctly blue sclera and hearing loss. It has autosomal dominant inheritance, and occurs in 1 per 30 000 live births. Fractures may be obvious from birth. Hearing impairment is the result of otosclerosis and affects most patients from the fifth decade, but is rare in the first decade. Some families have dentinogenesis imperfecta – with yellow transparent teeth that are fragile. There is spontaneous improvement with puberty. X-rays show generalized osteopenia, evidence of previous fractures and callus formation at the site of new bone formation. The skull X-ray shows wormian bones.

#### **Osteogenesis imperfecta type II**

This lethal syndrome is characterized by low birthweight and typical radiological findings of crumpled bones and beaded ribs. Although autosomal recessive in a few cases, most cases are autosomal dominant new mutations. It affects 1 per 60 000 live births; 50% are stillborn, the remainder dying soon after birth from respiratory difficulty because of a defective thoracic cage. It is worth looking at a picture of the lethal form. X-rays show multiple fracture of the ribs, often beaded, and crumpled (accordion-like) appearance of the long bones.

## **Osteogenesis imperfecta type III**

This syndrome is characterized by severe bone fragility and multiple fractures in the newborn period which lead to progressive skeletal deformity. The sclera may be bluish at birth, but become less blue with age. It is autosomal recessive with clinical variability suggesting genetic heterogeneity. Few patients survive into adult life. Radiographs show generalized osteopenia and multiple fractures, without the beading or crumpling of the ribs seen in type II.

## **Osteogenesis imperfecta type IV**

This syndrome is characterized by osteoporosis leading to bone fragility without the other features of type I. The sclera may be bluish at birth but become less blue as the patient matures. Inheritance is autosomal dominant. Variable age of onset and variable number of fractures, there is spontaneous improvement with puberty. Radiographs show generalized osteopenia and fractures, but these are generally less than the other forms of osteogenesis imperfecta.

## **Management**

For osteogenesis imperfecta type II no therapeutic intervention is helpful. For other forms, careful nursing of the newborn may prevent excessive fractures. Beyond the newborn period, aggressive orthopaedic treatment is the mainstay of treatment aimed at prompt splinting of fractures and correction of deformities. Bisphosphonates such as pamidronate have been shown to be useful. Genetic counselling is important. Reliable prenatal diagnosis is not available for all forms of osteogenesis imperfecta, although severely affected fetuses may be confidently recognized by X-rays, ultrasound scanning and biochemistry.

## **5.2 Osteopetrosis**

Osteopetrosis (marble bone disease, Albers–Schönberg disease) is characterized by a generalized increase in skeletal density. There are multiple types. The most important two are listed below.

### **Osteopetrosis congenita**

This presents in infancy (autosomal recessive) with faltering growth, hypocalcaemia, anaemia, thrombocytopenia and, rarely, fractures. Bone encroaching on the marrow cavity leads to extramedullary haematopoiesis. Optic atrophy and blindness are common, secondary to bone pressure. Diagnosis is by skeletal survey. Bone marrow transplantation can be curative.

### **Osteopetrosis tarda**

This presents in later childhood, usually with fractures, and manifestations are less severe and treatment is symptomatic.

## 5.3 Osteoporosis

- This can be idiopathic
- Most commonly secondary to corticosteroid use
- Seen in conditions causing decreased mobility such as cerebral palsy, neuromuscular diseases
- Dual energy X-ray absorptiometry (DXA) scan for bone mineral density
- Can cause pathological fractures, particularly of vertebrae
- Treat with calcium/vitamin D and bisphosphonates

## 5.4 Hemihypertrophy

This is often difficult to recognize. It may involve the whole of one side of the body, or be limited in extent, e.g. to just one leg. It may be congenital, in which case the tissues are structurally and functionally normal. It has been associated with learning disability, ipsilateral paired internal organs, and rarely with Wilms tumours or adrenal carcinomas.

Hemihypertrophy can be confused with regional overgrowth secondary to neurofibromatosis type 1, haemangiomas and lymphangiomas.

### **Beckwith–Wiedemann syndrome**

A fetal overgrowth syndrome, mapped to gene locus 11p15.5.

Clinically the three major features are:

1. Pre- and/or postnatal overgrowth (>90th centile)
2. Macroglossia
3. Abdominal wall defects

The minor defects are:

- Characteristic ear signs (ear lobe creases or posterior helical pits)
- Facial naevus flammeus
- Hypoglycaemia
- Organomegaly
- Hemihypertrophy.

The diagnosis is based on:

- Three major features, or
- Two major plus three or more minor features.

Infants are more likely to be delivered prematurely, 35% before 35 weeks. Exomphalos occurs in 50% of cases. Hypoglycaemia, which is usually mild and transient, occurs in 50%. Deaths from

Beckwith–Wiedemann syndrome can occur in infancy and are mainly caused by problems related to prematurity or congenital cardiac defects (<10%).

During childhood, the dysmorphic features become less apparent, although the macroglossia may cause problems with feeding, with speech and occasionally with obstructive apnoea. Surgical tongue reduction may be required in severe cases.

Overgrowth is most marked in the first few years and is associated with an advanced bone age. It tends to slow down in late childhood, and most adults are <97th centile. Hemihypertrophy occurs in 25% of cases. Visceromegaly is common and neoplasia occurs in 5%, most commonly with Wilms tumour followed by adrenocortical carcinoma, hepatoblastoma and neuroblastoma, those children with hemihypertrophy being the most at risk. By adolescence, the majority lead a normal life. There is controversy about abdominal tumour screening which some centres advocate should be by regular abdominal palpation and others by regular ultrasound examination or both.

## 5.5 Hypermobility

- The most common cause of musculoskeletal complaints in childhood related to muscular weakness in association with hypermobile joints
- Causes joint pain and occasionally swelling after exercise
- Improves with age
- Differential diagnosis includes Ehlers–Danlos syndrome (skin fragility and hyperextensibility, and joint hyperextensibility) and Marfan syndrome
- Management is exercise to build up strength and reassurance

## 5.6 Toe walking

- Can be a normal finding up until 3 years of age, especially in hypermobile patients; splint ankle because of over-supination/-pronation
- Neurological disorders include cerebral palsy, Duchenne muscular dystrophy, spinal cord problems, congenital shortening of the Achilles tendon
- Leg-length discrepancy
- Habit

## 5.7 Foot drop

- Variety of causes
- Patient has a stepping gait and lifts the affected limb high to avoid scraping the foot on the floor
- The patient is unable to walk on the heel
- Possible causes:
  - Lateral popliteal nerve palsy (look for signs of injury below and lateral to the affected knee)
  - Peroneal muscle atrophy



- Poliomyelitis

## 5.8 Reflex sympathetic dystrophy

- Autonomic nerve dysfunction in a limb results in severe immobilization because of pain
- Osteoporosis is associated
- Physiotherapy to remobilize is the best treatment

## 5.9 Non-accidental injury

- Non-accidental injury can present as musculoskeletal complaints, frequently seen with bruising
- Fractures – especially spiral or metaphyseal – more commonly in the under-3 age group
- Periosteal reactions from rotation injury
- Dislocations, especially of the elbow

## 5.10 Back pain

### Differential diagnosis

- Hypermobility with core weakness very common now, even in young children
- Trauma
- Spondylolisthesis/disc herniation
- Discitis
- Tuberculosis
- Leukaemia
- Enthesitis-related arthritis – sacroiliitis initially later lumbar
- Osteoid osteoma/Ewing tumour

### Investigations

- Radiograph
- Bone scan
- MRI
- FBC, ESR

## 5.11 Torticollis

### Common causes

- Sternomastoid tumour

- Vertebral anomalies
- Muscular spasm related to trapezius weakness – common now
- Pharyngitis with lymphadenopathy
- Retropharyngeal abscess
- Sandifer syndrome/gastro-oesophageal reflux
- Spinal tumours
- Posterior fossa tumours
- Atlantoaxial instability especially in Down syndrome
- Juvenile idiopathic arthritis – systemic onset and polyarticular

## 6. FURTHER READING

Ansell BM, Rudge S, Schaller JG (1991). *A Colour Atlas of Paediatric Rheumatology*. Aylesbury: Wolfe.

Cassidy JT, Petty RE, Laxer R, Lindsley C (2011). *Textbook of Pediatric Rheumatology*, 6th edn. New York: WB Saunders.

Isenberg DA, Miller JJ (1999). *Adolescent Rheumatology*. London: Martin Dunitz.

Mier RJ, Brower TJ (1994). *Paediatric Orthopaedics*. Dordrecht, The Netherlands: Kluwer Academic.

Brogan PA, Foster HE (2011). *The Oxford Handbook of Paediatric Rheumatology*. Oxford; Oxford University Press.

## **CONTENTS**

### **1. Study design**

- [1.1 Research questions](#)
- [1.2 Confounding](#)
- [1.3 Different types of study](#)
- [1.4 Bias](#)

### **2. Distributions**

- [2.1 Outcome measures](#)
- [2.2 Summarizing variables](#)
- [2.3 Summarizing differences between two groups](#)

### **3. Confidence intervals**

- [3.1 Standard error \(SE or SEM\)](#)

### **4. Significance tests**

- [4.1 Null hypotheses and  \$p\$  values](#)
- [4.2 Significance, power and sample size](#)
- [4.3 Types of tests](#)
- [4.4 The relationship between  \$p\$  values and confidence intervals](#)

### **5. Correlation and regression**

- [5.1 Correlation coefficients](#)
- [5.2 Linear regression](#)

### **6. Screening tests**

## **7. Things to look out for**

[7.1 Using inappropriate summaries for numeric data](#)

[7.2 Not dealing properly with missing data](#)

[7.3 Non-independent measurements treated as independent](#)

[7.4 Multiple testing without adjustment](#)

[7.5 Patients acting as their own controls](#)

[7.6 Testing group changes independently](#)

## **8. Further reading**

---

# Statistics

---

## 1. STUDY DESIGN

### 1.1 Research questions

A research study should always be designed to answer a pre-specified research question. Most commonly the question relates to a comparison between two groups. For example:

- Does taking folic acid early in pregnancy prevent neural tube defects?
- Is a new inhaled steroid better than current treatment for improving lung function among cystic fibrosis patients?
- Is low birthweight associated with hypertension in later life?

The question should be specific enough to be answerable. For example, ‘How do I cure diabetes?’ and ‘What are the problems associated with diabetes?’ are too broad.

An acronym that is sometimes used to help make sure a question specific is **PICO**. This stands for **p**atient, **i**ntervention, **c**omparison, **o**utcome.

Although this cannot be applied to all research questions, it is a useful breakdown that may assist. An explanation of each part is as follows:

**P**: what is the patient or problem or population?

Describe the group or groups to which the question applies.

**I**: intervention or exposure or test being considered

**C**: is there a comparative intervention? Or perhaps comparison is with healthy individuals?

**O**: what is the outcome measure? What are you trying to identify differences in?

For example:

**P**: pregnant women; **I**: folic acid; **C**: no folic acid; **O**: neural tube defect – yes/no

**P**: cystic fibrosis patients; **I**: new inhaled steroid; **C**: current treatment; **O**: lung function

**P**: newborns; **I**: low birthweight; **C**: not low birthweight; **O**: hypertension

To answer the specified research question, samples of the relevant populations are taken. For

example: pregnant women, cystic fibrosis patients, low-birthweight and normal birthweight individuals.

Based on what is seen in those samples, inferences are made about the populations from which they were randomly sampled. For example:

- If the women in the sample taking folic acid have fewer neural tube defects, it may be inferred that taking folic acid during pregnancy will reduce the incidence of neural tube defects in the population
- If among our sample of cystic fibrosis patients, those taking steroids have better lung function on average than those on current treatment, the inference might be that steroids improve lung function among cystic fibrosis patients in general.
- If there is a difference in hypertensive rates between samples of individuals who were and were not of low birthweight, it may be inferred that birthweight is associated with later hypertension in the population in general.

## 1.2 Confounding

Confounding may be an important source of error. A confounding factor is a background variable (i.e. something not of direct interest) that:

- is different between the groups being compared, and
  - affects the outcome being studied
- For example: In a study to compare the effect of folic acid supplementation in early pregnancy on neural tube defects, age will be a confounding factor if:
- either the folic acid or placebo group tends to consist of older women, and
  - older women are more, or less, likely to have a child with a neural tube defect
- When studying the effects of a new inhaled steroid against standard therapy for cystic fibrosis patients, disease severity will be a confounder if:
    - one of the groups (new steroid/standard therapy) consists of more severely affected patients, and
    - disease severity affects the outcome measure (lung function)
  - In the comparison of hypertension rates between low and not low birthweight, social class will be a confounder if:
    - the low-birthweight babies are more likely to have lower social class, and
    - social class is associated with the risk of hypertension

If a difference is found between the groups (folic acid/placebo, new steroid/standard therapy and low/normal birthweight) we will not know whether the differences are, respectively, the results of folic acid or age, of the potency of the new steroid or severity of disease in the patient, or of birthweight or social class, respectively.

Confounding may be avoided by matching individuals in the groups according to potential confounders. For example, we could age match folic acid and placebo pairs or deliberately recruit individuals of low and normal birthweight from similar social classes.

## 1.3 Different types of study

Studies are either observational or experimental. Different types of study may be used to address the same research question, although some will give more evidence than others. The choice of study design may be influenced by ethical, financial and feasibility issues.

### Observational studies

The researchers have observed and reported what happens. They have not changed anything, merely observed and documented what occurs in one or more groups of individuals, e.g. those who do and do not take folic acid early in pregnancy.

When an observational study compares two groups, it may be categorized as being a **cohort**, **case–control** or **cross-sectional** study. These studies consider differences between the groups in the future, in the past and at the present time respectively.

A **cohort** study will usually categorize currently healthy individuals according to some feature (such as drinking alcohol or not, smoking or not, eating a high-fat diet or not) and follow the groups forward in time to see whether one group is more likely to develop disease.

A **case–control** study will usually compare diseased and healthy groups and look back in time to see what they have done differently in the past that may have led to disease.

Another type of observational study is an **ecological** study. Here the unit of analysis is a population rather than an individual and association across different populations is investigated, e.g. an ecological study may look at the association between prematurity and childhood cancer rates in different countries to see whether those countries with higher prematurity rates also have higher levels of childhood cancers.

### Experimental studies

In experimental studies, individuals are assigned to groups by the investigator, e.g. pregnant women will be assigned to take either folic acid or a placebo; cystic fibrosis patients will be assigned to either the new or current treatment. In both of these examples the second group is known as a **control group**.

Note that a control group does not necessarily consist of normal healthy individuals. In the second example, the control group comprises cystic fibrosis patients on standard therapy.

Individuals should be randomized to groups to remove any potential bias. **Randomization** means that each patient has the same chance of being assigned to either of the groups, regardless of their personal characteristics. Note that random does not mean haphazard or systematic.

Randomization may be adjusted to ensure that the groups are balanced with respect to potential confounders. It may be stratified or within pair-matched pairs, e.g.:

- Pairs of pregnant women of the same age may be selected and one of each pair randomly assigned folic acid supplementation
- Pairs of cystic fibrosis patients of similar disease severity with one randomly selected to receive the new steroid whereas the other receives standard therapy.

Experimental studies may be:

- **Double blind** – neither the patient nor the researcher assessing the patients (or the treating clinician) knows which treatment the patient has been randomized to receive
- **Single blind** – either the patient or the researcher/clinician does not know (usually the patient)
- **Unblinded** (or open) – both the patient and the researcher/clinician know

It is preferable that studies are blinded because knowledge of treatment may affect the outcome and introduce a bias in the results.

**Allocation concealment** means that the allocation (to treatment or control) is not known before the individual is entered into the study.

**Clinical trials** are experimental studies.

### Crossover studies

In a **crossover** (or **within-patient**) study, each patient receives treatment and placebo in a random order. Fewer patients are needed than the comparable **parallel trials** (in which different individuals are allocated to the two treatment groups) because many between-patient confounders can be removed, e.g. even though pairs of cystic fibrosis patients may be chosen and randomized to groups on the basis of their disease severity, this does not ensure that the groups will be of similar age or sex.

Crossover studies are only suitable for chronic disorders that are not cured but for which treatment may give temporary relief, e.g. it would not be feasible to do a crossover trial of folic acid in pregnancy.

There should be no **carryover effect** of the treatment from one treatment period to the next. Sometimes it is necessary to leave a gap between the end of the first treatment and the start of the next to ensure that there is no overlap. This gap period is known as a **washout period**.

### Intention-to-treat analysis

With experimental studies, individuals are allocated to different treatments or interventions. Allocation is usually randomized and the purpose is to ensure that the groups obtaining the different treatments are not biased in ways that might confound the study results. However, some individuals may not adhere to the 'treatment' to which they are allocated, e.g. there may be an active treatment to be compared with placebo and some of those allocated to the active treatment do not take the medicine. Furthermore, some of those allocated to placebo may decide to take active treatment anyway. Although it may be tempting to move these individuals across to the other group for analysis



(so that the 'active treatment' group becomes those allocated to active treatment who complied plus the 'placebo' patients who decided to take active control anyway, and the 'placebo' group includes those allocated to active treatment who did not take the treatment), this is not good practice. Those who did not adhere to their allocated treatments may be biased in a way that affects the results.

The study was designed as experimental to avoid bias caused by allowing personal preference to determine treatment. Hence, the outcomes for the two allocation groups (those allocated to active treatment and those allocated to control) should be compared irrespective of how many of each actually adhered to their allocation. This is known as **intention-to-treat analysis**.

It may also be useful to perform a **per protocol** analysis whereby those who do not adhere to the allocated treatment are excluded from the analyses. Although this may be informative, it should be noted that the results may be biased.

## Comparing study designs

There may be many ways to address a particular research question, e.g. if we wish to determine whether smoking is causally associated with lung cancer, any of the following would potentially address this question:

- **Ecological studies** might show a relationship between levels of smoking and lung cancer rates in different countries/regions
- **Cross-sectional studies** would show that those with lung cancer are more likely to be current smokers
- **Case-control studies** would select a group of lung cancer patients and a group of healthy controls to see how they differed in previous behaviours (i.e. smoking)
- A **cohort study** would select groups of currently healthy smokers and non-smokers and follow these forward in time to see whether one group was more likely to develop lung cancer.
- A **randomized controlled trial** (RCT) would randomly allocate healthy individuals to smoke or not and then see who developed lung cancer

This last study would of course be unethical!

In all of the study types there is the potential for confounding, e.g. if the smokers are more likely to drink alcohol. In the observational studies (first four) there is more likelihood of there being confounding factors that may not even be considered or measured. It may be that the tendency to smoke is associated with some other factor (such as drinking alcohol or dietary factors) that is the true causation of lung cancer occurring (hence smoking would be falsely declared the causal agent). The RCT (last study) is not immune from confounding but it is less likely that there will be hidden confounders.

If a potential confounder such as drinking alcohol is known about, this can be avoided by suitable design manipulation. For the observational studies this will involve selecting groups similar with respect to alcohol consumption to compare. For the RCT the randomization can be stratified according to alcohol consumption or randomization to smoking or not can take place within pairs

matched for alcohol consumption.

## 1.4 Bias

Bias may take many forms and can invalidate the study results if not taken into account properly when drawing conclusions.

**Sampling bias** occurs if some members of the eligible population are more likely to be included in the sample than others.

**Retrospective recall bias** occurs if one group is more likely to recall events than the other. This is often a problem with case–control studies.

**Publication bias** is important when considering systematic reviews. This is the process whereby some studies (usually those showing significant differences) are more likely to be published.

## 2. DISTRIBUTIONS

### 2.1 Outcome measurements

Usually the research question relates to a single primary outcome measure although there may be many secondary outcomes.

If the measure is **reliable** then it will be measured consistently under different conditions if the underlying value has not changed, e.g. does the assessment of a patient depend on who made the measurement? Or the time of day that it was made (assuming that the patient has not changed the condition)? If there is variation in measurement that is not associated with change in the patient but other factors (such as who made the measurement or when), then the measure is unreliable.

A **valid** measurement will give an accurate assessment, e.g. assessment of gestational age via date of last menstrual period is less valid than ultrasound dating using fetal measurements early in pregnancy.

Outcomes are either **numeric** or **categoric**. It is important to identify the type of each outcome because this will determine the summary measures and statistical tests that should be used.

**Numeric** measurements are made on a number scale, e.g. height, weight, blood pressure, IgG level.

**Categoric** measurements put individuals into one of two or more categories, e.g. positive/negative, low/medium/high, disease/none, ethnic group, hair colour. If there are only two categories then the variable is **binary**.

### 2.2 Summarizing variables

If the variable is **numeric**, the distribution of the variable will be either **symmetrical** or **skewed** (tails off unevenly in one direction), e.g. the bar chart in Figure 24.1 shows the heights of a set of individuals and is reasonably symmetrical, whereas the distribution in Figure 24.2 of their income levels is upwardly skewed.

When the distribution is symmetrical and bell shaped (i.e. even tailing off in either direction), the variable is said to be **normally distributed** (or to follow a **normal distribution**), e.g. height as illustrated in Figure 24.1.

Appropriate summaries of the **average** and **spread** of the variable are as follows:

- **Mean** and **standard deviation** if the distribution of the variable is *symmetrical*
- **Median** and **interquartile range (IQR)** or **range** if the distribution is *skewed*
- It is not uncommon to find skewed data incorrectly summarized using the mean
- If the mean and standard deviation are valid measurements, then the interval:

(mean  $\pm$  2 standard deviations)

should give a range that will contain most (approximately 95%) of the values

Figure 24.1

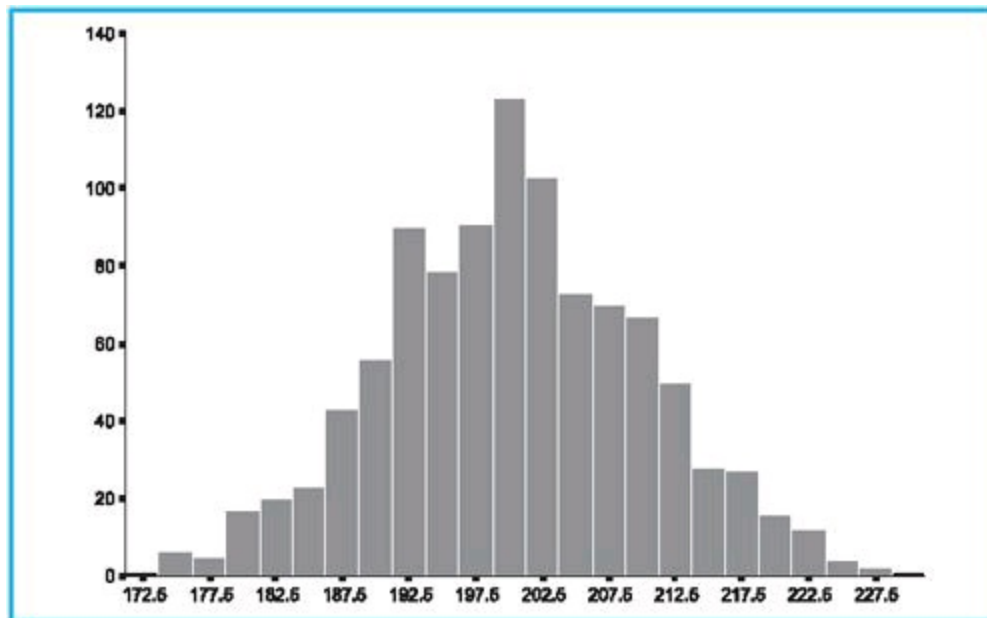
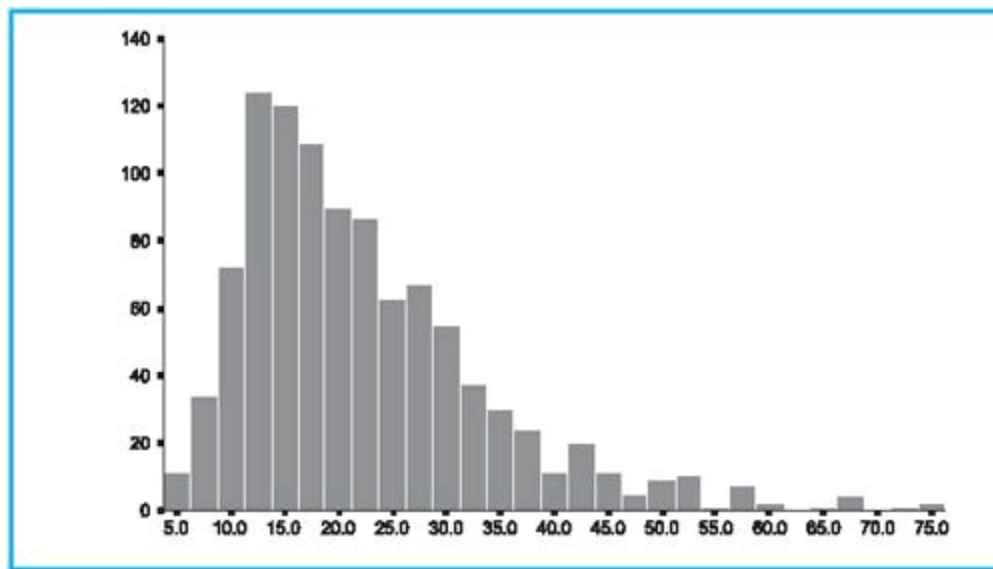


Figure 24.2



For example, forced expiratory volume in 1 second ( $FEV_1$ ) is measured in 100 students. The mean value for this group is 4.5 litres with a standard deviation of 0.5 l. If the values are normally distributed then approximately 95% of the values lie in the range  $(4.5 \pm 2(0.5)) = (4.5 \pm 1) = (3.5, 5.5 \text{ l})$ .

If the variable is **binary**, the number in one category can be expressed as:

- A **proportion** by dividing by the total number
- A **percentage (%)** by multiplying the proportion by 100
- The **odds** by dividing by the number in the other category

For example, if 30 of 50 test positive, the proportion testing positive is 0.6, the percentage is 60% and the odds of testing positive are  $30/20 = 1.5$ .

## 2.3 Summarizing differences between two groups

Many studies collect information on two groups and make comparisons between them, e.g. groups given new or standard treatment, diseased individuals versus healthy controls.

The appropriate comparison statistic to use depends on the type of variable being compared. If the variable is *numeric*, then the **difference in means** or medians will provide a suitable summary to compare the groups.

If the variable is *binary*, there are several different summaries that can be used. These are:

- The **difference in proportions or percentages** in the two groups – this is sometimes known as the **risk difference** or **absolute risk reduction (ARR)**. A value of zero indicates no difference between groups
- The **number needed to treat (NNT)** – which is the inverse of the ARR
- The proportion in one group may be divided by the proportion in the other – this gives the **relative**

**difference** between the proportions in each group and is known as the **relative risk** or **risk ratio (RR)**. A value of 1 indicates no difference between groups

- An approximation to the relative risk is used for case–control studies. This is known as the **odds ratio**

For the research questions given in Section 1.1, the suitable summaries of the outcomes may be:

- The risk of neural tube defect (number of cases divided by the number of women studied) among women taking folic acid and those who do not. The relative risk (risk in group taking folic acid divided by the risk in those who take placebo treatment) would give a measure of how effective the intervention is in preventing neural tube defects
- The difference in average (mean or median) lung function between those given the new steroid and those given standard therapy will provide a measure of the effectiveness of the new treatment compared with standard
- The difference in percentages of individuals developing hypertension between those who were low birthweight and normal birthweight (ARR) would provide a useful summary measure

## 3. CONFIDENCE INTERVALS

### 3.1 Standard error

Any estimate of a population measurement (mean, proportion, difference in percentages, etc.) should be presented with a measure of precision. This measure of precision will depend on the sample size and will take the form of a **standard error** (SE or standard error of the mean, SEM) or, preferably, a **95% confidence interval**.

Larger samples give more precise estimates, smaller standard errors and narrower confidence intervals.

The confidence interval is calculated using the standard error:

- The interval (**mean  $\pm$  1.96 SE**) is a **95% confidence interval** for the population value
- The interval (**mean  $\pm$  2 SE**) is an **approximate 95% confidence interval** for the population value

We are 95% confident that the true value lies inside the interval. The 95% confidence interval (sometimes abbreviated to confidence interval, 95% CI or CI) gives the range of population parameters that the sample leads us to believe are possible, e.g. suppose that 10.75% more of the low-birthweight group suffer hypertension at some point (compared with those not of low birthweight) and the 95% CI for this difference is (7.25, 14.25%). We would be reasonably confident (95%) that, in the population (from which these individuals were a random sample), the increase in hypertension among those of low birthweight would be at least 7.25% (about 1 in 14) and could be as much as 14.25% (about 1 in 7).

Compare this with the interpretation if smaller samples had been taken and the 95% CI for the

difference of 10.75% had therefore been wider, say (−12.0, 33.5%). In this case we would not be sure whether there was a positive association between low birthweight and hypertension. Our samples are compatible (at 95% CI) with 12% fewer and 33.5% more of the low birthweight individuals being hypertensive. Since the interval contains 0%, the data are compatible with no difference in hypertension rates.

Note the difference between the *standard deviation* and the *standard error*:

- **Standard deviation (SD)** gives a measure of the **spread** of numeric data values
- **Standard error (SE)** is a measure of **how precisely** the sample estimate approximates the population value and can apply to both numeric and categoric outcomes

For example, consider again the FEV<sub>1</sub> measurements from 100 students with mean 4.5 l and SD 0.5 l. The SE can be calculated by combining the SD and the sample size to be 0.05 (details not given).

Hence, an approximate 95% CI for the population mean FEV<sub>1</sub> is given by:

$$(4.5 \pm 2(0.05)) = (4.5 \pm 0.1) = 4.4, 4.6 \text{ l}$$

i.e. we are 95% confident that the population mean FEV<sub>1</sub> of students lies in the range 4.4–4.6 l.

Confidence intervals can similarly be constructed around any summary statistic, e.g. the difference between two means, a single proportion or percentage, the difference between two proportions. The SE always gives a measure of the precision of the sample estimate and is smaller for larger sample sizes.

## 4. SIGNIFICANCE TESTS

**Statistical significance tests**, or **hypothesis tests**, use the sample data to assess how likely some specified **null hypothesis** is to be correct. The measure of ‘how likely’ is given by a probability known as the ***p* value**.

### 4.1 Null hypotheses and *p* values

Usually, the **null hypothesis** is that there is ‘**no difference**’ between the groups, e.g. to answer the research questions in Section 1.1 we test the following null hypotheses:

- There is no difference in the incidence of fetuses with neural tube defects between the groups of pregnant women who do and do not take folic acid supplements
- The distribution of lung function is the same in asthma patients who receive the new inhaled steroid and those on current treatment
- Hypertension rates do not differ according to birthweight.

Even if these null hypotheses were true we would not expect the averages or proportions in our

sample groups to be identical. As a result of random variation there will be some difference.

The  **$p$  value** is the probability of observing a difference of that magnitude if the null hypothesis is true.

As the  $p$  value is a probability, it takes values between 0 and 1. Values near to 0 suggest that the null hypothesis is unlikely to be true. The smaller the  $p$  value the more significant the result:

- $p = 0.05$ , the result is significant at 5%

The sample difference had a 1 in 20 chance of occurring if the null hypothesis were true.

- $p = 0.01$ , the result is significant at 1%

The sample difference had a 1 in 100 chance of occurring if the null hypothesis were true.

**Note that statistical significance is not the same as clinical significance.**

Although a study may show that the results from drug A are statistically significantly better than for drug B we have to consider:

- The magnitude of the improvement
- The costs
- The ease of administration
- The potential side effects of the two drugs, etc.

before deciding that the result is clinically significant and that drug A should be introduced in preference to drug B.

## 4.2 Significance, power and sample size

The study sample may or may not be compatible with the null hypothesis being true.

If the  $p$  value is small then there is a low probability of observing the samples if the null hypothesis is true, and this would lead us to 'reject' the null hypothesis. A  $p$  value not near to 0 shows that the data are compatible with the null hypothesis, e.g.:

- If there are many more babies with neural tube defects among the group not taking folic acid, then this is unlikely to happen given the null hypothesis (no difference in incidence) and the  $p$  value will be low (close to zero). This would lead us to reject the null hypothesis and believe that there is an association between incidence and folic acid consumption
- If the asthma patients receiving the new inhaled steroid have a similar average lung function to those in the current treatment arm of the trial, this is likely to happen given the null hypothesis (distributions of lung function do not differ) and the  $p$  value will be large (close to 1). We would therefore have no reason to reject the null; our data are compatible with the null being true (i.e. no

effect of the new treatment)

Hence, on the basis of the study results, we may decide to disbelieve (or reject) the null hypothesis. In reality, the null hypothesis either is or is not true. This gives the fourfold situation illustrated below:

Decision based on study results	Null hypothesis:	
	True	False
'Accept' null hypothesis	OK	(II)
'Reject' null hypothesis	(I)	OK

Hence the study may lead to the wrong conclusions:

- A low (significant)  $p$  value (close to zero) may lead us to disbelieve (or reject) the null hypothesis when it is actually true – see box above. This is known as a type I error

For example, suppose, for the comparison of neural tube defects,  $p = 0.001$ . This would imply that the difference in percentage defects observed would have occurred only once in 1000 times if there really were no association with folic acid. Although very unlikely it is not impossible to have occurred by chance (for 1 trial in 1000 it would do).

- The  $p$  value may be high (non-significant, away from zero) when the null hypothesis is false – see box above. This is known as a type II error

For example: in Section 3.1 the second example CI for difference in percentage hypertensive between low and not low birthweight individuals was  $(-12.0, 33.5\%)$  which is compatible with 0 ( $p$  value will be large, say 0.82) but we cannot exclude the possibility that as many as a third more of the low-birthweight become hypertensive. The CI is wide because the study is small and hence inconclusive; the study may have failed to detect a difference that is there.

The **power** of a study is the probability (usually expressed as a percentage) of correctly rejecting the null hypothesis when it is false.

Larger differences between the groups can be detected with greater power. The power to identify correctly a difference of a certain size can be increased by increasing the sample size. Small samples often lead to type II errors (i.e. there is not sufficient power to detect differences of clinical importance).

In practice there is a grey area between accepting and rejecting the null hypothesis. The decision will be made in the light of the  $p$  value obtained. We should not draw different conclusions based on a  $p$  value of 0.051 compared with a value of 0.049. The  $p$  value is a probability – as it gets smaller the less likely it is that the null hypothesis is true.

## 4.3 Types of tests



There are many different significance tests and the appropriate one to use depends on the *type of outcome* being compared, the *number of groups* being compared and, in the case of two groups, *whether there is a pairing* between groups (e.g. age- and sex-matched pairs of diseased individuals and healthy controls; the same patient assessed when on two different treatments as part of a crossover trial).

For comparing two groups the correct tests are:

- Binary outcome – **chi-squared** ( $\chi^2$ ) or **Fisher exact test** (if small numbers)
- Numeric normally distributed outcome – **t-test**, **paired t-test** if samples are paired/matched
- Numeric, non-normally distributed outcome (or small numbers) – **Mann–Whitney U-test**

To compare a normally distributed numeric outcome between *more than two groups* then **analysis of variance (ANOVA)** can be used, e.g. to compare heights between five different ethnic groups.

If the outcome is non-normally distributed, or numbers are very small, then **Kruskal–Wallis ANOVA** is appropriate, e.g. to compare incomes between the ethnic groups.

*If adjustment is to be made for confounders* before comparing the main outcome between groups, then **regression analyses** are appropriate. Adjusted estimates of effect are obtained, and these can be tested against ‘no effect’. A *p* value is obtained for the test of whether the sample is compatible with the model coefficient being 0.

## 4.4 The relationship between *p* values and confidence intervals

The confidence intervals show the range of population scenarios that the sample data are compatible with, whereas the corresponding significance test assesses compatibility with no difference (the null hypothesis) only.

If the *p* value is  $<0.05$ , the 95% CI will not contain 0 (or 1 in the case of odds ratios/relative risks), as both show that the data are not compatible with no difference between groups.

Similarly, if the *p* value is  $>0.05$ , the 95% CI will contain 0 (or 1 depending on the summary measure), indicating no significant difference (i.e. compatibility of the sample with there being no difference between groups).

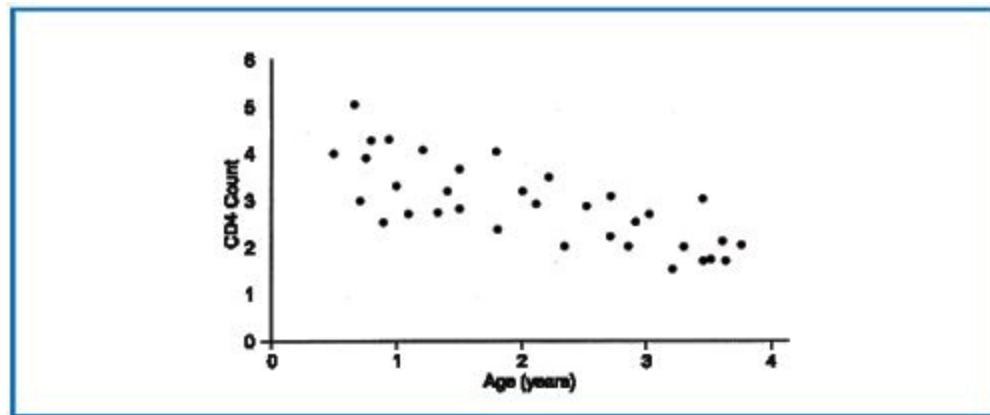
## 5. CORRELATION AND REGRESSION

Sometimes measurements are made on two continuous variables for each study subject, e.g.:

- CD4 count and age
- Blood pressure and weight
- FEV<sub>1</sub> and height

The aim may be to quantify the relationship between the two variables. The data can be displayed in a scatter plot and this will show the main features of the data.

**Figure 24.3** Scatter plot of CD4 count versus age



## 5.1 Correlation coefficients

The **correlation coefficient** (sometimes called the **Pearson coefficient of linear correlation**) is denoted by  $r$  and indicates how closely the points lie to a line.

If  $r$  takes values between  $-1$  and  $+1$ , the closer it is to  $0$  the less linear the association between the two variables. (Note that the variables may be strongly associated but not linearly.)

Negative values of  $r$  indicate that one variable decreases as the other increases (e.g. CD4 count falls with age).

Values of  $-1$  or  $+1$  show that the variables are perfectly linearly related, i.e. the scatter plot points lie on a straight line.

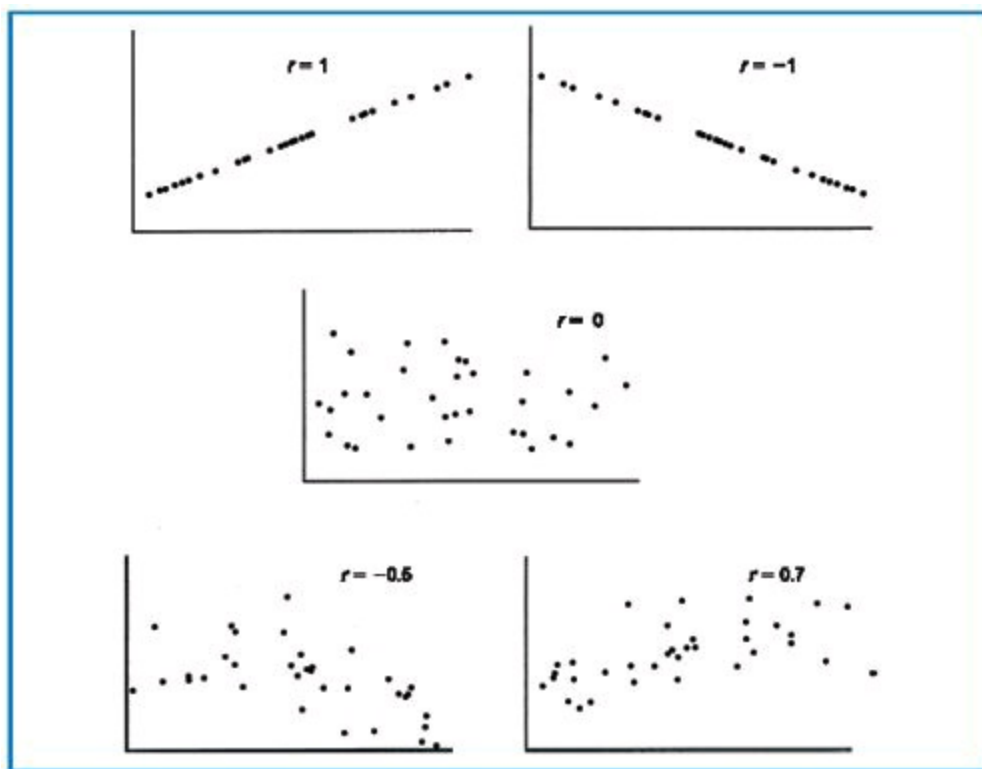
Correlation coefficients:

- Show how one variable increases or decreases as the other variable increases
- Do not give information about the size of the increase or decrease
- Do not give a measure of agreement

The Pearson  $r$  is a parametric correlation coefficient. The **Spearman rank correlation** is the most commonly used **non-parametric correlation coefficient**:

- *Parametric correlation coefficients* quantify the extent of any linear increase or decrease
- *Non-parametric correlation coefficients* quantify the extent of any tendency for one variable to increase or decrease as the other increases (e.g. exponential increase or decline, increasing in steps)

**Figure 24.4** Scatter plots with different correlation coefficients



A *p* value attached to a parametric correlation coefficient shows how likely it is that there is no linear association between the two variables.

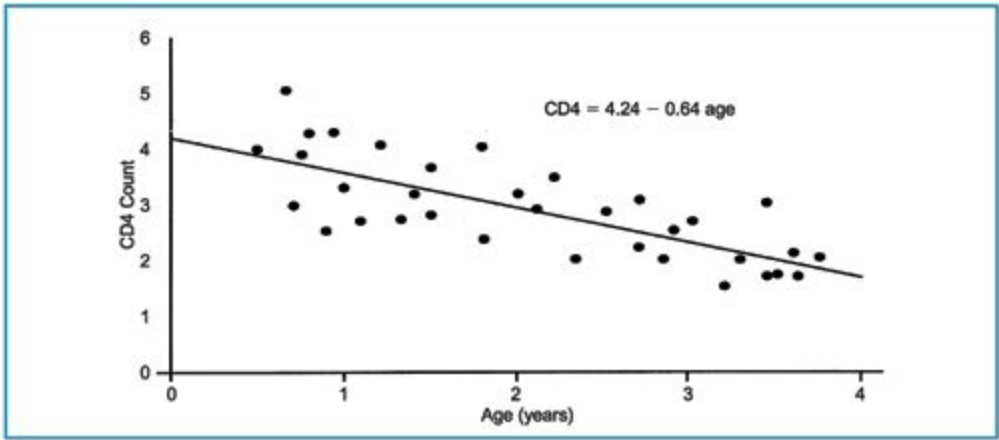
A significant correlation does not imply cause and effect.

Note that a correlation of 0 does not necessarily imply no relationship, merely that there is no *linear* association.

## 5.2 Linear regression

A **regression equation** may be used to predict one variable from others. If there is a single numeric predictor then this can be represented as a line on the scatter plot (Figure 24.5).

Figure 24.5 CD4 count versus age



The plot shows that the CD4 count falls on average with increasing age. The regression equation ( $CD4 = 4.24 - [0.64 \times \text{age}]$ ) quantifies that relationship. As age increases by 1 year, the CD4 count

falls on average by 0.64. Ideally this estimate should be presented with a confidence interval to show the range of population scenarios with which the sample is compatible.

## 6. SCREENING TESTS

Screening tests are often used to identify individuals at risk of disease. Individuals who are positive on screening may be investigated further to determine whether they actually have the disease:

- Some of those who are screen positive will not have the disease
- Some of those who have the disease may be missed by the screen (i.e. test negative)

This gives a fourfold situation as shown in the box below ( $a$ ,  $b$ ,  $c$  and  $d$  are the numbers of individuals who fall into each of the four categories).

	Diseased	Disease free	Total
Screening test result:			
Positive (indicating possible disease)	$a$	$b$	$a + b$
Negative	$c$	$d$	$c + d$
<b>Total</b>	$a + c$	$a + d$	$a + b + c + d$

There are several summary measures that are often used to quantify how good a screening test is:

- **Sensitivity** is the proportion of true positives correctly identified by the test:  
 $a/(a + c)$
- **Specificity** is the proportion of true negatives correctly identified by the test:  
 $d/(b + d)$
- **Positive predictive value** is the proportion of those who test positive who actually have the disease,  $a/(a + b)$
- **Negative predictive value** is the proportion of those who test negative who do not have the disease,  $d/(c + d)$

For all of these measures, larger values are associated with better screening tests. The values are usually multiplied by 100 and presented as percentages, e.g. if 75 out of 100 individuals with the disease test positive, the sensitivity is  $75/100 = 0.75$ ; expressed as a percentage this gives a sensitivity of 75%.

Note that the positive and negative predictive values depend on the **prevalence** of the disease, i.e. the proportion of the total that have disease:  $(a + c)/(a + b + c + d)$  – and may vary from population to

population.

## Likelihood ratios

These compare the probability of the test result given that the individual has the disease to the probability of the result occurring if they are disease free. They are calculated from the sensitivity and specificity and are not dependent on disease prevalence.

- The likelihood ratio (LR) for a positive test result  $LR+ = \text{Sensitivity} / (1 - \text{Specificity})$
- The likelihood ratio for a negative test result,  $LR- = \text{Specificity} / (1 - \text{Sensitivity})$

Likelihood ratios can be multiplied by pre-test odds to give post-test odds, e.g. a screening test is applied to patients with and without disease X. Of 100 who have the disease, 60 test positive; of 200 without the disease, only 20 test positive. From this information the following table can be constructed:

Test result	Disease X	Disease free
Positive (indicating possible disease)	60	20
Negative	40	180

The following can, therefore, be estimated from this sample of 300 individuals:

- Sensitivity =  $60/100 = 0.6$  or 60%
- Specificity =  $180/200 = 0.9$  or 90%
- $LR+ = 0.6 / (1 - 0.9) = 6$
- $LR- = (1 - 0.6) / 0.9 = 0.44$
- The positive predictive value is  $60 / (60 + 20) = 0.75$  or 75% (i.e. 75% of those who test positive actually have the disease in this sample)
- The prevalence of the disease in this sample is:  $(60 + 40) / (100 + 200) = 0.33$  or 33%

If a particular patient had a probability of 60% of having the disease (based on age, other risk factors, etc.) then their prior odds are 60/40 (for every 60 individuals of this type who have disease, 40 do not) = 1.5.

The posterior odds of the patient having the disease will be determined by the result of the screening test thus:

- If the test is positive ( $LR+$ ) then the odds of having the disease will be

$$1.5 \times 6 = 9$$

- If the test is negative ( $LR-$ ), the odds will be

$$1.5 \times 0.44 = 0.66$$

Note that, as expected, the odds of having the disease rise if the test is positive and fall if the test is negative.

A posterior odds of 9 means that the patient is nine times more likely to have the disease than not, which equates to a probability of 9/10 or 0.9 (as opposed to 0.6 before testing).

A posterior odds of 0.66 equates to a probability of  $0.66/1.66$ , or 0.4 (as opposed to 0.6 before testing).

## 7. THINGS TO LOOK OUT FOR

Sometimes mistakes are made when the techniques outlined in the previous sections are applied and this section gives an overview of those most commonly seen.

### 7.1 Using inappropriate summaries for numeric data

The use of means with skewed data has already been highlighted (see [Section 3.2](#)). All of the data may not be needed to identify this problem if means (SD) are given for very skewed data. We can check whether the limits  $\text{mean} \pm 2 \text{ SD}$  are valid; if not then this implies skewness and inappropriate usage of the summaries.

For example: suppose the mean (SD) casual annual income for a group of students is given as £2023 (£1450). Then:

$$\text{Mean} + 2\text{SD} = 2023 + 2(1450) = £4923$$

$$\text{Mean} - 2\text{SD} = 2023 - 2(1450) = -£877$$

The second limit (−£877) is invalid because the students would not have earned a negative amount.

The distribution of earnings is probably upwardly skewed with a few students earning relatively large amounts. Hence the mean is unrepresentative of the group; the median (IQR) would be a better summary.

### 7.2 Not dealing properly with missing data

Missing data can occur for many reasons. Often the study aims to collect information on a variety of background factors and perhaps also multiple outcomes. It is not uncommon to find a relatively large proportion of the study participants with one or more missing pieces of information. Sometimes the missing values are replaced by the mean of the available data on that variable or, if repeat measurements are made, by the last available measurement (this latter case is known as the ‘last

observation carried forward' or LOCF). Neither of these is a good option because they pretend that the data are available when they are not and the resulting estimates will be too precise.

Another approach is to create a 'missing' category and include this in the analysis. Surprisingly, this may introduce bias in the other estimates and is therefore not recommended.

A **complete case** analysis may be undertaken whereby any individuals with missing data on any variables are excluded from the analyses. This is often the default option used by statistical software packages. However, this is not a good option because the dataset that remains (and on which the analyses will be performed) may be greatly reduced and also biased (individuals with complete data may differ from the others in a way that is associated with outcome).

The best way to deal with missing data is via **multiple imputation**, whereby the values are imputed and a random element incorporated so that precision is not artificially increased.

## 7.3 Non-independent measurements treated as independent

Most statistical analyses make inferences based on the assumption that the sample measurements of a given variable are independent. Non-independence occurs most commonly:

- when individuals are measured serially
- within cluster randomized trials – where groups of individuals within the same unit (e.g. classes of children, families, GP units, districts, hospital wards) are randomized en masse to different treatments

When data are grouped in this way, the information obtained is less than what would have been if data were collected from independent individuals, e.g. taking 1 measure from each of 50 individuals will always give more information about that measurement and its variation between individuals than having 10 measures from each of 5 individuals. As we are usually concerned with between-individual variation in outcomes in research studies (How well does a treatment work on average? What is the average effect of disease on individuals? etc.), then this is a problem if not properly addressed. If there is any form of non-independence, this must be taken into account in the analyses, otherwise the estimates presented will be overly precise.

**Multilevel, hierarchical or random effects** models are appropriate for dealing with non-independent sets of outcome measurements.

## 7.4 Multiple testing without adjustment

A  $p$  value gives the probability of the samples differing by the amount observed if some null hypothesis were true (see [Section 4.1](#)). A  $p$  value of 0.05 would mean that a difference that large would be found only for 5% (or 1 in 20) samples if the null were true. A  $p$  value of 0.001 would mean that it would only occur in 1 in 1000 samples. However, this is based on only one outcome

being compared between groups. If 20 outcomes were compared, then we would expect 1 of them to yield a  $p$  value of 0.05 by chance. If 10 independent outcomes were tested the chance that at least one would be significant at 5% is 0.41.

If multiple outcomes are compared then the significance levels should be adjusted to take account of this. A **Bonferroni adjustment** to the  $p$  value will do this.

## Subgroup analyses

Another form of multiple testing is when data are considered within subgroups, e.g. a blood pressure treatment may be found to be non-significant overall but effective in the subgroup of females. Sometimes, many subgroupings are considered and only one or two significant differences reported whereas the statistically non-significant differences are not.

The problems with subgroup analyses are those of multiple testing, with the additional problem of some of the sample sizes being very small. With small samples there is a danger that clinically important differences will be missed. The study will have been designed to have sufficient power to detect a clinically important effect with the total sample size, and the subgroups will not have as much power.

Subgroup differences in outcome can be investigated validly using regression models incorporating interaction terms to determine whether the differences in outcome between subgroups are statistically significant. For example, the difference in outcome may be significant in females and insignificant in males, but this does not necessarily imply that the difference in outcome is significantly different between males and females, which is what an interaction term formally tests.

## 7.5 Patients acting as their own controls

Sometimes measurements are made pre- and post-treatment with the idea that patients ‘act as their own controls’. It is assumed that, if the patients improve pre- → post-, this is due to treatment. However, this is not a good study design because there is no measure of how the patients would have fared over the same time period in the absence of treatment. It is possible that the patients would have improved anyway. Most patient outcome measures (happiness, blood pressure, general wellbeing, etc.) will fluctuate over time due purely to random variation rather than any overall trend. Often, patients are enrolled into trials when their disease is particularly bad (e.g. when blood pressure is very high) because they may seek care and/or be willing to try new treatments when symptoms are worse. As they are at a bad point, given random fluctuation, we may expect that they would improve in the following time period regardless of any treatment. Similarly, if recruited when they were particularly well, we might expect them to become worse (due to random fluctuation) in the following time period. Hence, observing a difference in a group pre- and post-treatment does not imply causality because there is no control group against which to measure the effect of treatment.

## 7.6 Testing group changes independently



Sometimes individuals are measured at two time points and a control group is similarly assessed. In this scenario there are two sets of differences to compare: e.g. those for a group pre- → post-treatment and the other for a comparable group receiving placebo measured twice over a similar time-frame. Sometimes the significance of the change pre- → post- in each group is calculated separately using paired tests and the  $p$  values for the two tests compared. However, showing a significant difference in one group and not in the other does not imply a significant difference between groups.

Depending on the distribution of the within-pair differences (whether or not normally distributed), the significance of any average change (pre- → post-) between the treated and placebo groups should be assessed using either a two-sample  $t$ -test or a Mann–Whitney U test. This analysis will show whether the changes in one group are significantly different to the changes in the other.

## 8. FURTHER READING

Altman DG. *Practical Statistics for Medical Research*. London: Chapman & Hall, 2006.

Altman DG, Machin D, Bryant TN, Gardner MJ. *Statistics with Confidence*. London: BMJ Books, 2005.

Bland M. *An Introduction to Medical Statistics*. Oxford: Oxford University Press, 2008.

Kirkwood BR, Sterne JAC. *Essential Medical Statistics*. Oxford: Blackwell Science, 2005.

Machin D, Campbell MJ, Walters SJ. *Medical Statistics: A textbook for the health sciences*. Chichester: Wiley & Sons, 2007.

Peacock J, Kerry S. *Presenting Medical Statistics from Proposal to Publication: A step-by-step guide*. Oxford: Oxford University Press, 2007.

Peat J, Barton B. *Medical Statistics: A guide to data analysis and critical appraisal*. Oxford: BMJ Books, Blackwell Publishing, 2007.

Petrie A, Sabin C. *Medical Statistics at a Glance*. Oxford: Blackwell Publishing, 2005.

---

# Chapter 25

## Surgery

*Merrill McHoney*

---

## CONTENTS

### Neonatal surgery

#### 1. Antenatal diagnosis of surgical conditions

#### 2. Congenital oesophageal anomalies

2.1 Oesophageal atresia and tracheo-oesophageal fistula

2.2 Dying spells

#### 3. Neonatal intestinal obstruction

#### 4. Intestinal atresia

4.1 Duodenal obstruction

4.2 Jejunoileal atresia

4.3 Colonic atresia

4.4 Pyloric atresia

#### 5. Malrotation

#### 6. Meconium ileus

#### 7. Hirschsprung disease

#### 8. Anorectal malformations

8.1 Imperforate anus

#### 9. Necrotizing enterocolitis

## **10. Biliary atresia**

## **11. Anterior wall defects**

[11.1 Gastroschisis](#)

[11.2 Exomphalos](#)

## **12. Congenital diaphragmatic hernia**

[12.1 Eventration of the diaphragm](#)

## **13. Malformations of the airway and lungs**

[13.1 Choanal atresia](#)

[13.2 Laryngeal cleft](#)

[13.3 Congenital lobar emphysema](#)

[13.4 Congenital cystic adenomatoid malformation](#)

[13.5 Pulmonary sequestration](#)

[13.6 Bronchogenic cyst](#)

## **14. Neonatal tumours**

[14.1 Teratoma](#)

[14.2 Sacrococcygeal teratoma](#)

## **15. Spina bifida**

## **16. Miscellaneous conditions**

[16.1 Antenatal torsion](#)

[16.2 Accessory digit](#)

## **General paediatric surgery**

## **17. Head and neck surgery**

[17.1 Ranula](#)

[17.2 Lymphatic malformation](#)

[17.3 Thyroglossal cyst](#)

[17.4 Preauricular pits](#)

[17.5 Branchial arch remnants](#)

[17.6 Cervical lymphadenopathy](#)

[17.7 Haemangiomas and arteriovenous malformations](#)

[17.8 Central venous access](#)

## **18. Thoracic surgery**

[18.1 Congenital malformations](#)

[18.2 Chest wall deformities](#)

[18.3 Oesophageal foreign bodies](#)

[18.4 Caustic ingestion](#)

[18.5 Parapneumonic effusions](#)

## **[19. Gastrointestinal surgery](#)**

[19.1 Abdominal wall herniae](#)

[19.2 Pyloric stenosis](#)

[19.3 Gastrostomy](#)

[19.4 Gastro-oesophageal reflux disease](#)

[19.5 Intussusception](#)

[19.6 Appendicitis](#)

[19.7 Meckel diverticulum](#)

[19.8 Undescended testis](#)

[19.9 Testicular torsion](#)

[19.10 Phimosis](#)

[19.11 Hypospadias](#)

## **[20. Further reading](#)**

---

# Neonatal surgery

---

## 1. ANTENATAL DIAGNOSIS OF SURGICAL CONDITIONS

- Identify pathology and assess severity/complications
- Search for other associated anomalies
- *In utero* intervention – thoracoamniotic shunt for a massive congenital cystic adenomatoid malformation with significant mediastinal shift and hydrops
- Modify pregnancy monitoring – gastroschisis (in third trimester have weekly ultrasounds and twice-weekly cardiotocographs for late intrauterine death, have an expectation of preterm labour)
- Parental counselling – opportunity for karyotyping, consideration of termination of pregnancy, information regarding early postnatal care and surgery/outcome
- Plan delivery/immediate neonatal and surgical care

## 2. CONGENITAL OESOPHAGEAL ANOMALIES

### 2.1 Oesophageal atresia and tracheo-oesophageal fistula

Oesophageal atresia (OA) and tracheo-oesophageal fistula (TOF) comprise faulty separation of the primitive embryonic trachea from the foregut (future oesophagus). Incidence is 1 in 3000 to 1 in 3500. Many are associated with preterm labour as a result of polyhydramnios.

- 85% – blind proximal oesophageal pouch with a tracheo-oesophageal fistula to the distal pouch
- 5–10% – pure oesophageal atresia (long gap)
- 5% – H fistula (tracheo-oesophageal) without an oesophageal atresia
- Rare – oesophageal atresia with upper pouch fistula, or upper and lower pouch fistulae

Associated with tracheomalacia (weakness of tracheal wall due to deficient cartilaginous development) with resultant narrowing of trachea (gives rise to ‘TOF cough’).

Also associated with VACTERL anomalies (vertebral **a**nal, **c**ardiac, **t**racheal, **o**esophageal, **r**enal and **l**imb).

### Diagnosis

- Antenatal scan – polyhydramnios, absent gastric bubble, distended upper oesophagus (interrupted foetal swallowing)
- After birth – excessive salivation, choking because of aspiration after every feed, respiratory distress with or without cyanotic episodes. Other associated anomalies are seen in 30–50%
- Confirmation – failure to pass a large-bore (10 French scale) nasogastric tube (with chest radiograph to demonstrate that the nasogastric tube is not coiled in the oesophagus) ± bronchoscopy at surgery to confirm location of lower pouch fistula and to exclude upper pouch fistula and laryngeal cleft
- Contrast swallow is not indicated (risk of aspiration)

## Management

- Stop feeds and aspirate upper pouch
- Respiratory support as required – avoid bag and mask ventilation to reduce gastric distension
- Replogle tube – sited in the proximal pouch – double-lumen tube (with side holes) placed on low-pressure continuous suction preventing suction of the intestinal mucosa against the tube. Larger lumen requires flushing with 1–2 ml saline to prevent blockage with tenacious secretions
- Antibiotics if evidence of pulmonary aspiration
- Minimal handling – reduces air swallowing from crying
- Echocardiogram – ideally before surgery, especially if infant is cyanotic, there is significant cardiac murmur or infant requires cardiac support. May have duct-dependent lesion requiring prostaglandin E<sub>1</sub> infusion and early cardiac opinion. Repair the oesophageal atresia/tracheo-oesophageal fistula when stable
- Renal ultrasound – if urine is passed, this can be delayed until after surgery
- Spinal ultrasound – to exclude cord tethering (will be asymptomatic in the neonatal period)
- Karyotype – if infant is dysmorphic or has other system anomalies
- Parental counselling

## Surgery

- Emergency ligation of fistula – seen in the premature neonate with respiratory distress syndrome
- Common anatomy (OA + TOF) – right thoracotomy, ligation of the fistula and primary end-to-end anastomosis of OA with early extubation. Trans-anastomotic tube passed for feeding. A ‘tight’ anastomosis may require a period of paralysis and ventilation
- Long-gap – may require complex and staged procedures

## Complications

- Anastomotic leak
- Recurrent fistula
- Stricture (at anastomosis)
- Tracheomalacia
- Gastro-oesophageal reflux
- Abnormal oesophageal motility

- Missed upper pouch fistula
- Reflex bradycardia  $\pm$  respiratory arrest – vagal stimulation from a distending food bolus
- Chylothorax

### **Acute life-threatening episodes (dying spells)**

Episodes of respiratory distress associated with breath holding and or cyanosis. May have several, sometime overlapping causes, with difficulty identifying main cause.

- Missed upper pouch fistula or recurrent fistula. Will require re-do surgery
- Severe tracheomalacia exacerbated during feeding or crying, with complete airway collapse, cyanosis and cessation of stridulous breathing, followed by loss of consciousness, relaxation of the airway, and recovery. May require surgical intervention (aortopexy)
- Gastro-oesophageal reflux disease: investigate with contrast study, pH study or endoscopy. Surgical management warranted

### **Outcome**

- Overall survival rate is 85–95%
- Highest risk – birth weight <1500 g, severe associated anomalies, major congenital heart defect, ventilator dependency

## **3. NEONATAL INTESTINAL OBSTRUCTION**

Incidence 1 in 500–1000 live births. About half will have an atresia or stenosis. After delivery, swallowed air will reach the small bowel within 30 min, the colon by 3–4 h and the rectum by 6–8 h.

### **Clinical presentation**

- May have clinical suspicion from antenatal ultrasound – proximal bowel dilatation, ‘double bubble’, echogenic bowel loops (meconium ileus), polyhydramnios
- Most present shortly after birth with abdominal distension (delayed in distal obstruction), large nasogastric aspirate (>50 ml initial volume), bilious vomiting, delayed passage of meconium (>24 h)
- Premature neonate – delayed passage of meconium expected, bilious nasogastric aspirate may be the result of intestinal immaturity or sepsis
- Passage of flatus will exclude an atresia

### **Common causes**

- Malrotation with volvulus
- Duodenal atresia, stenosis, extrinsic compression
- Jejunoileal atresia, or stenosis
- Meconium ileus (simple, complicated)

- Meconium plug obstruction
- Hirschsprung disease
- Ileus secondary to sepsis, paralysis/ventilation/medication
- Inguinal hernia (incarcerated)
- Anorectal malformation

## **Less common causes**

- Small left colon syndrome (infant of mother who has diabetes, typical isolated small left colon on contrast study, which is usually curative)
- Megacystis-microcolon-intestinal hypoperistalsis syndrome (see below)
- Colonic atresia

## **Radiological diagnosis**

- Abdominal radiograph
  - Proximal obstruction – a few dilated loops, mainly in the upper abdomen
  - Distal – numerous throughout most of abdomen (paucity of rectal gas suggests distal colonic or rectal obstruction)
- Partial obstruction will allow some distal gas, often mixed with meconium
- Inspect for peritoneal/scrotal calcification (meconium peritonitis/prenatal perforation)
- Water-soluble lower gastrointestinal contrast – to distinguish distal bowel obstruction (Hirschsprung disease, ileal atresia, meconium ileus/plug)
- Water-soluble upper gastrointestinal contrast – to investigate intestinal rotation abnormalities

## **General management**

- Nasogastric tube and gastric decompression
- Replace nasogastric losses with 0.9% NaCl with KCl, ml for ml
- Intravenous fluid replacement
- Consider rectal decompression or washout after surgical consultation/review
- Broad-spectrum antibiotics if there is suspicion of intestinal ischaemia (red/shiny/oedematous abdominal wall, abdominal tenderness, absent bowel sounds, metabolic acidosis) or perforation

## **Megacystis–microcolon–intestinal hypoperistalsis syndrome**

A rare, usually fatal, condition with degenerative smooth muscle changes in the bowel and renal tract. Abdominal distension from lax abdominal muscles and a dilated bladder. Incomplete intestinal rotation, microcolon (barium enema) with poor peristalsis. Ultrasound demonstrates hydronephrosis and megacystis (differentiate from Hirschsprung disease).

## **4. INTESTINAL ATRESIA**



Development of the intestine is completed by 10 weeks gestation, foregut, midgut and hindgut forming with their respective blood supplies (coeliac, superior mesenteric and inferior mesenteric arteries). Liver and pancreas arise from the developing duodenum.

- Duodenal – failed vacuolization and recanalization of the developing duodenum during weeks 8–10 of gestation. Greater association with other major anomalies and development anomalies of the pancreas/biliary tree
- Jejunoileal/colonic – follows a late intrauterine mesenteric vascular event with sterile ischaemia of the bowel (resorbed). Associated with abdominal/mechanical abnormalities (gastroschisis, mucoviscidosis in meconium ileus, with volvulus  $\pm$  cystic fibrosis, volvulus secondary to malrotation)
- Relative frequency – jejunal > duodenal > ileal > colonic > pyloric
- More proximal atresia – earlier vomiting, less abdominal distension
- Distal atresia – delayed presentation of vomiting, more abdominal distension, greater fluid and electrolyte abnormality
- Abdominal radiograph – number of dilated bowel loops suggests the approximate level of atresia
- A neonate with an intestinal atresia (as opposed to other causes of intestinal obstruction) will fail to pass any flatus, even after rectal examination

Note: The presence of a few dilated bowel loops is suggestive of a proximal small bowel atresia. It may however represent an infant with little distal midgut following a major intrauterine mesenteric vascular event which may be incompatible with life and only identified at surgery.

## 4.1 Duodenal obstruction

- Incidence is 1 in 2500 live births
- Intrinsic obstruction – atresia, stenosis, web
- Extrinsic obstruction – annular pancreas, malrotation, pre-duodenal portal vein
- 50% are associated with other anomalies – cardiac, genitourinary, anorectal, OA  $\pm$  TOF, malrotation, congenital diaphragmatic hernia, vertebral
- 30–40% are associated with trisomy 21
- 80% are periampullary (bilious vomiting), 20% preampullary (non-bilious vomiting)

### Prenatal diagnosis

- Polyhydramnios in up to 75%
- Intrauterine growth restriction, premature delivery in up to 50%
- Dilated stomach and proximal duodenum (‘double bubble’) on antenatal ultrasound
- Features suggesting trisomy 21 (nuchal translucency)

### Postnatal diagnosis

- Index of suspicion – trisomy 21, oesophageal atresia
- Vomiting – especially bilious, initial nasogastric aspirate >20 ml with no other obvious cause

- Abdominal radiograph – ‘double bubble’

**Caution** – suggestive ‘double bubble’ with some distal gas may be duodenal stenosis or bifid biliary duct but must exclude malrotation  $\pm$  volvulus (see below).

## Medical management

- Nasogastric insertion for gastric decompression, intravenous volume replacement
- Assess for other anomalies  $\pm$  karyotype if dysmorphic

## Surgical care

- Laparotomy – primary repair (duodenoduodenostomy)
- Postoperative nasogastric replacement – initial aspirate volume may be high (100–150 ml/day), until duodenal stasis is resolved. Replace ml for ml with 0.9% NaCl (with added KCl)

## Complications

- Related to co-morbid pathology – cardiac, chromosomal
- Prolonged bilious aspirates because of poor motility from delayed duodenal peristalsis
- Blind loop syndrome – chronic duodenal dilatation and secondary bacterial overgrowth

## 4.2 Jejunoileal atresia

- Incidence – up to 1 in 1000–1500 live births
- Multiple small bowel atresias – jejunal (67%), ileal (25%)
- Few associations with chromosomal abnormalities or other system anomalies
- Bowel length variable – may be foreshortened, risk of short bowel

## Postnatal presentation

- Persistent bilious vomiting
- Abdominal distension – most marked with distal atresia, visible bowel loops, fluid and electrolyte disturbance
- Meconium – varies from normal colour to grey plugs of mucus

## Radiology

- Dilated bowel loops – number of loops suggests level of atresia (proximal versus distal)
  - Note: in the neonate, large and small bowel are indistinguishable on radiograph because of the poor development of the haustral folds and valvulae conniventes
- Abdominal calcification – meconium peritonitis secondary to an intrauterine perforation

## Medical management

- Nasogastric tube insertion for gastric decompression, volume replacement
- Cardiorespiratory support as required

## Surgery

- Laparotomy – assessment of bowel length and viability, exclusive of multiple atresias, and other pathology, primary anastomosis (more than one may be required)  $\pm$  proximal stoma

## Complications

- Anastomotic leak
- Stricture formation
- Nutritional – vitamin B<sub>12</sub> and bile salt absorption affected from loss of terminal ileum
- Short bowel syndrome – following catastrophic small bowel loss, the survival prognosis depends partly on the presence of the ileocaecal valve (30 cm with, 50 cm without). The premature neonate has a greater capacity for functional adaptation

### 4.3 Colonic atresia

Rare (5% of all atresias), with an incidence of 1 in 1500 to 20 000 live births. Right colon is most commonly affected. Associated with anorectal malformation, Hirschsprung disease, small bowel atresia, renal/cardiac/limb/cerebral abnormalities.

### 4.4 Pyloric atresia

Rare (<1% of all atresias), 50% are associated with polyhydramnios, non-bilious vomiting from birth, epigastric distension, single gastric bubble on radiograph, respiratory symptoms are common. Associated with epidermolysis bullosa.

## 5. MALROTATION

Interference with the normal return of the fetal intestine into the abdominal cavity.

- Population incidence of 1 in 125 (post-mortem examinations). Lifetime risk of symptoms 1 in 60 of these (i.e. about 1 in 6000 of the general population)
- Associated with other abnormalities – exomphalos, gastroschisis, diaphragmatic hernia, cardiac anomalies associated with visceral heterotaxy
- Presents with green bile-stained vomiting within the first week (55%), or by 1 month (80%) with only sporadic cases thereafter

- May exist with other abnormalities – exomphalos, gastroschisis, diaphragmatic hernia, cardiac anomalies associated with visceral heterotaxy
- Small bowel predominantly in the right abdomen
- The narrow mesentery is prone to kinking, and in the event of a volvulus, the entire midgut blood supply may be compromised, bowel infarction may occur in 6 h with resulting loss of the midgut

## Radiology

- **Gas pattern on plain abdominal radiograph may be normal**
- Signs of proximal intestinal obstruction  $\pm$  asymmetrical and/or sparse distal gas pattern

## Contrast study

- Failure of the duodenojejunal junction to cross the midline on upper gastrointestinal contrast and lie to the left of the spine
- ‘Corkscrew’ sign if small bowel volvulus is present
- Dilated proximal duodenum with failure of passage of contrast into the second part of the duodenum
- Barium enema may show caecum/appendix in the right hypochondrium – an unreliable sign alone as the normal neonatal colon is mobile

**Caution** – bilious vomiting mandates an urgent water-soluble upper gastrointestinal contrast study at any time of the day/night (even if the infant is well, without abdominal distension or tenderness, with a ‘normal’ plain abdominal radiograph and with normal biochemistry/haematology profiles). Clinical deterioration with abdominal tenderness, cardiorespiratory collapse, metabolic and lactic acidosis, upper/lower gastrointestinal bleeding is a late sign of compromised bowel and impending death. This is a life-threatening emergency.

## Surgery

- Adequate resuscitation
- Nasogastric decompression, fluid, broad-spectrum antibiotics
- Laparotomy – confirm diagnosis, untwist volvulus, assess bowel viability/length, resect necrotic bowel, proximal stoma/second-look laparotomy for uncertain viability

## 6. MECONIUM ILEUS

- Incidence of 1 in 1000–2000 live births
- 80–90% will have cystic fibrosis but only 15% of infants with cystic fibrosis will present with meconium ileus
- Thick mucus and viscid meconium, lower lactase/sucrase levels, more albumin and less pancreatic enzyme
- Obstruction of the distended meconium-filled terminal ileum. Small, unused colon, inspissated pellets of colourless mucus

- Complications occur in 50% – antenatal volvulus of the distended ileum with atresia, meconium peritonitis or pseudocyst formation
- Antenatal perforation is sterile, postnatal perforation is complicated by bacterial contamination and systemic sepsis

## Diagnosis

- Uncomplicated – abdominal distension, bilious vomiting, failure to pass meconium, ‘doughy’ mass on palpation within 24–48 h of birth
- Complicated – abdominal wall erythema, oedema, meconium staining – suggests prenatal perforation
- Cystic fibrosis screen

## Radiology

- Simple – proximal bowel dilatation, few air-filled loops, meconium mottling (‘soap bubble’, ‘ground glass’) often in the right lower quadrant
- Complicated – calcification (extravasation of meconium into the peritoneal cavity), massive bowel dilatation (atresia), displaced bowel loops (pseudocyst), ascites
- Gastrografin enema can be repeated after diagnosis in a therapeutic manner
- Alternative – *N*-acetylcysteine (Mucomyst) by nasogastric tube or per rectum (breaks down disulphide bridges in tenacious meconium) can be used as adjunctive therapy

**Caution** – Gastrografin is hyperosmolar and draws fluid into the terminal ileum from the intravascular space, softening the meconium. Adequate fluid resuscitation is vital before and during use to prevent potentially catastrophic cardiovascular collapse.

## Surgery

- Simple meconium ileus, following unsuccessful therapeutic enema, laparotomy, instillation of *N*-acetylcysteine, or enterostomy and irrigation
- Complicated meconium ileus may require surgical correction of an atresia, volvulus, pseudocyst, perforation
- Primary anastomosis ± temporary proximal stoma

## Complications

- With cystic fibrosis, 1-year survival rate is 75–90%
- Late complications – distal intestinal obstruction syndrome (10%), appendicitis (5%), intussusception (2%), rectal prolapse (10–30%)

## Meconium plug obstruction

Failure to pass meconium or only a small inspissated plug, passed after per rectum examination, and

followed by normal meconium. Usually require therapeutic enema. Exclude cystic fibrosis and Hirschsprung disease, and investigate for underlying cause.

## 7. HIRSCHSPRUNG DISEASE

Absence of ganglion cells in the myenteric plexus of the most distal bowel; male incidence greater than female. Occurs in 1 in 5000 births.

- Gene on chromosome 10, *RET* proto-oncogene
- Long-segment Hirschsprung disease is familial (4–7%) with equal sex incidence
- Associated with trisomy 21 (5–15% reports vary – between 2 and 15% have Down syndrome), high frequency of other congenital abnormalities, including multiple endocrine neoplasia
- Transition zone in the rectosigmoid junction is most common (>75%)
- Total colonic/small bowel involvement (5–10%) – poor prognosis

### Presentation

- Usually presents in infancy – poor feeding, abdominal distension, delayed passage of meconium, bilious vomiting
- Radiological evidence of distal intestinal obstruction with absence of rectal gas
- Explosive decompression following rectal examination (passage of gas excludes atresia)
- First presentation may be with acute enterocolitis (red, tender, shiny abdomen) ± severe systemic collapse. Diarrhoea is offensive ± blood or ischaemic mucosa. May require emergency defunctioning colostomy
- Enterocolitis can occur pre- or post-surgery, some associated with *Clostridium difficile* enterotoxin

### Initial management

- Nil-by-mouth, intravenous fluids, correction of electrolyte abnormalities, high colonic washouts to decompress the bowel (feeding tube, not balloon catheter)
- Fluid resuscitation + broad-spectrum antibiotics if presenting with enterocolitis
- Poor result – usually technical but may suggest long segment disease

### Diagnosis

- Contrast enema – identify transition zone, exclude other pathology
- Definitive test is suction rectal biopsy for histology

### Surgery

- Several options of pull-through operations exist (Duhamel, Soave-Swenson) that involve excision of the involved colon, anastomosis with innervated proximal bowel (propulsion); a small part of

the involved rectum remains (sensation and sphincter innervations)

- Still have risk of enterocolitis following surgery (treated as above)

## Outcome

- Incidence of enterocolitis: 5–25%, increased in trisomy 21 (29–54%), associated cardiac defects, total colonic involvement (15–25%). Overall mortality rate from enterocolitis: 5–25%
- Surgical management for anastomotic leak, pelvic abscess, intestinal obstruction
- Medical management of soiling, constipation, frequent loose stools

## 8. ANORECTAL MALFORMATIONS

### 8.1 Imperforate anus

- Incidence of 1 in 4000–5000 live births
- Association with maternal diabetes
- Male (60%) – most commonly imperforate anus with rectourethral fistula
- Female (40%) – most commonly imperforate anus with rectovestibular fistula
- Imperforate anus without a fistula is uncommon (5%)
- Associated defects are common

## Presentation

- Clinical examination
- Failure to pass meconium, abdominal distension, bilious vomiting (late sign)
- Passage of meconium or bubbles per urethra/vagina (high lesion)
- Meconium staining beneath perineal skin (low lesion)
- Following identification of other VACTERL anomalies (vertebral, **anal**, cardiac, tracheal, oesophageal, renal and limb)

## Initial management

- Nil-by-mouth, intravenous, nasogastric decompression (passage of tube will exclude OA/TOF).
- Systematic examination, chest/abdomen/sacral radiograph, echocardiogram, renal ultrasound, spinal ultrasound (exclude cord tethering), ± karyotype
- Prophylactic antibiotics until communication with renal tract is excluded (trimethoprim)
- Invertogram to assess level of rectal atresia (lateral shoot through, infant prone over a foam wedge, buttock elevated with a radio-opaque marker at the anal position). Thick meconium within distal bowel or straining (crying) will provide inaccurate results

## Surgery

- A primary operation (PSARP or posterior sagittal anorectoplasty) can be performed for low

lesions in the neonatal period

- Staged procedure for high lesions:
- Staged loop colostomy usually with 48 h for high lesions (dysfunctioning)
- Distal loopogram and micturating cystourethrogram to identify anatomy of rectum and communication with urinary tract (position of fistula  $\pm$  vesicoureteric reflux)
- PSARP
- Aim for colostomy closure after healed
- Various surgical options – may require complex staged procedures, urogenital surgery, dilatation of new anus, medical management of bowel control (including enema)

## Outcome

- Dependent on level of lesion, sacral development (S3, -4 and -5 required for urinary continence) and associated anomalies
- Low lesion – constipation (40%), soiling (15%), diarrhoea (5%)
- High lesion – constipation (35%), soiling (55%), diarrhoea (12%)

## 9. NECROTIZING ENTEROCOLITIS

Pathological response of the immature gastrointestinal tract to perinatal or postnatal injury. Usually seen in the first 2–3 weeks of life. Rapid and early introduction of non-breast-milk feeds, hyperosmolar feeds and bacterial infection are important aetiological factors. Progressive intestinal mucosal ischaemia, most commonly affecting the caecum, ascending colon and terminal ileum but can affect the entire intestinal tract.

### Risk factors

- Prematurity
- Intrauterine growth restriction
- Antepartum haemorrhage
- Perinatal asphyxia (absent or reversed end-diastolic umbilical vessel waveform)
- Respiratory distress syndrome
- Umbilical artery catheterization
- Polycythaemia
- Patent ductus arteriosus
- Premature rupture of membranes
- Sepsis

### Radiological signs of necrotizing enterocolitis (NEC)

- Thickened bowel loops (non-specific)
- Localised bowel distension
- Pneumatosis intestinalis (soap bubble appearance in wall of bowel); pathognomonic



## **Radiological signs of gastrointestinal perforation**

- ‘Football sign’ (central, oval abdominal lucency)
- Visible falciform ligament  $\pm$  an umbilical venous line *in situ*
- ‘Wrigler sign’ (visualization of both sides of the bowel wall)
- Gas outlining the liver (left lateral decubitus view with horizontal beam projection)
- Scrotal gas (via a patent processus vaginalis)
- ‘Triangles’ of gas between bowel loops
- Upper abdominal lucency, especially over the liver (anteroposterior supine film, vertical beam projection)

## **Medical management**

- Stop enteral feeds for 7–14 days (depending on severity of illness)
- Intravenous antibiotics (broad-spectrum, including metronidazole; consult local unit policy)
- Adequate intravenous analgesia
- Total parenteral nutrition
- Nasogastric tube, on free drainage with hourly aspiration and volume replacement
- Remove umbilical lines
- Regular abdominal radiographs to exclude perforation or the development of a fixed loop
- Needs to be distinguished from cows’ milk protein intolerance

## **Complications**

- Recurrence (10% of cases consider Hirschsprung disease)
- Perforation in 20–30%
- Overwhelming sepsis
- Disseminated intravascular coagulation
- Stricture formation – up to 20%. Consideration of contrast studies – assessment of possible strictures (intolerance of increasing feed volume, intestinal obstruction or recurrent bacterial translocation after clinical recovery)
- Short-bowel syndrome (following extensive surgical resection)
- Lactose intolerance –  $>0.5\%$  faecal reducing substances significant
- Overall mortality rate is still 20–30%

## **Surgical management**

- Indications – pneumoperitoneum, failure of maximal medical management, stricture formation, fixed loop  $\pm$  palpable mass
- Insertion of a peritoneal drain – may be life saving for a tense pneumoperitoneum compromising ventilation, but is not usually definitive
- Laparotomy – allows diagnosis to be confirmed, extent of disease to be assessed and peritoneal toilet to be performed and abscess cavities drained
- Localized resection with primary anastomosis

- Proximal diversion stoma  $\pm$  bowel resection
- Stoma formation – ileostomy or colostomy depending on extent/location of necrotizing enterocolitis
- May require more than one procedure, including stoma closure and stricture resection
- Spontaneous intestinal perforation is either a different entity to NEC or may represent a small subgroup of mild localized disease
- Usually no prodromal period of unstable or ‘septic’-looking baby
- Associated with non-steroidal anti-inflammatory use, which may be contributory
- No pneumatosis on abdominal radiograph
- Sudden abdominal distension and need for ventilation
- Laparotomy – perforation usually in terminal ileum with otherwise healthy looking bowel
- Localized resection with primary anastomosis feasible

## 10. BILIARY ATRESIA

Incidence is 1 in 8000–20 000 live births. It is the most common indication for liver transplantation in childhood.

- **Extrahepatic biliary atresia** – progressive obliteration of part or all of the extrahepatic ducts. Aetiology uncertain
- **Intrahepatic biliary atresia** – this is less common and can be either syndromic (Alagille syndrome) or non-syndromic

### Investigations

- Liver function tests (often normal enzymes with conjugated hyperbilirubinaemia), clotting
- Ultrasound (may be normal, gall bladder may be absent)
- Radionuclide technetium-99m-labelled iminodiacetic acid ( $[^{99m}\text{Tc}]\text{HDA}$ ) scan (unimpaired hepatic uptake of isotope but failure of excretion into the duodenum after 24 h)
- Liver biopsy
- Laparotomy – surgical cholangiography

### Treatment

- Hepatopertoenterostomy (Kasai procedure)
- Aim for surgery before the infant is 60 days old (high mortality from end-stage liver disease after this)
- Ursodeoxycholic acid to promote bile secretion, fat-soluble vitamin supplementation
- Postoperatively – high risk of cholecystitis (prompt treatment with intravenous antibiotics)
- Fat malabsorption, cirrhosis, liver failure
- Liver transplantation may be indicated

### Caroli disease

- Autosomal recessive, congenital cystic dilatation of the intrahepatic ducts
- Recurrent acute cholangitis, biliary lithiasis, risk of cholangiocarcinoma

## 11. ANTERIOR WALL DEFECTS

### 11.1 Gastroschisis

There is controversy regarding the aetiology but it is probably the result of the intrauterine rupture of the right vitelline artery and breakdown of the abdominal wall adjacent to the umbilicus.

- Incidence of 1 in 3000–6000 live births, trend increasing
- Typical infant – preterm, small for gestational age, lower maternal age, oligohydramnios, antenatal ingestion of aspirin, illegal drugs (vasoconstrictor side effects), alcohol
- Risk of late intrauterine deaths, monitor fetal movements, increased ultrasound and cardiotocogram in third trimester
- Vaginal delivery is not contraindicated
- Defect is lateral (usually to the right, 95%) to the intact umbilical cord
- Herniation of bowel without a covering sac, stomach, occasionally bladder, but rarely the liver
- Intestinal atresia is common, occurring in approximately 20% of cases. Short bowel may complicate outcome
- Rarely associated with lethal chromosomal or major structural abnormalities
- Can be confused with a ruptured exomphalos

### Management at delivery

- Wrap Clingfilm around entire trunk, covering exposed bowel and ensure infant is well supported in the midline to reduce temperature and fluid evaporative losses
- Large-bore nasogastric (NG) tube, intravenous fluids above normal rate. May need bolus to replace initial losses
- Regular visual assessment of bowel viability if closure is delayed, and during neonatal transfer

### Surgical management

- Undertaken promptly after delivery. May require staged surgical repair after initial silo application
- Total parenteral nutrition and trophic milk via nasogastric tube
- Delay in establishing feeds is related to poor intestinal motility – bilious NG aspirates, abdominal distension, failure to pass changed stool
- Repair of atresia may be deferred until abdominal closure is completed

### Outcome

- Morbidity is related to short bowel
- 10% risk of necrotizing enterocolitis

- Prognosis is usually good

## 11.2 Exomphalos

- Failure of closure of the abdomen at the umbilical ring
- Incidence is 1 in 5000 to 1 in 10 000 live births, trend is decreasing (partly related to termination of pregnancy following identification of other lethal structural or chromosomal abnormalities)
- 40–70% have associated abnormalities – chromosomal (trisomies 13, 18 and 21), cardiac (25%), genitourinary, gastrointestinal, craniofacial, pulmonary hypoplasia
- Syndromic associations – Beckwith–Wiedemann syndrome, prune-belly syndrome and pentalogy of Cantrell
- Antenatal karyotype analysis should be advocated, along with a more detailed anomaly scan. Parental counselling in cases with severe associated abnormalities may include elective termination

### Management at delivery

- Leave cord length long
- Cover exomphalos with Clingfilm, as per gastroschisis (reduce temperature/fluid evaporative loss)
- Support contents in the midline (vertically tie the umbilical cord to the overhead heater or incubator)
- Assess bowel colour through sac (initially transparent), look for blood (hepatic trauma), avoid sac rupture
- NG decompression, intravenous fluid/electrolyte resuscitation, temperature as per gastroschisis
- Clinical assessment – dysmorphic features (especially midline defects), karyotype, chest radiograph, echocardiogram, renal ultrasonography
- Early and regular blood glucose measurements (Beckwith–Wiedemann syndrome)
- Early surgical involvement

### Surgery

- Aim for reduction of abdominal contents and complete closure
- May require staged procedures
- Massive exomphalos (especially with small abdominal cavity) or infants with multiple abnormalities may be managed conservatively. Topical application of saline, to allow eschar formation and skin overgrowth. Delayed surgical management of massive ventral hernia some years later
- Meticulous fluid management

### Outcome

- Associated defects or chromosomal abnormalities have a major influence on survival
- 35% mortality, three times that of gastroschisis

## 12. CONGENITAL DIAPHRAGMATIC HERNIA

- Incidence is 1 in 2500 to 1 in 3500 live births
- Chromosomal abnormalities found in 5–30% of cases (trisomies 18 and 13 are most common)
- Serious associated anomalies in 40% live-born babies (cardiac and neural tube defects)
- Frequent association with intestinal fixation abnormalities including malrotation
- Associated lung hypoplasia
- Both lungs are structurally abnormal (ipsilateral > contralateral). This is the major determining factor in the outcome of babies born alive with congenital diaphragmatic hernia
- Left-sided is more common than the right (6:1)
- 90% are a posterolateral defect (Bochdalek hernia)
- Poor prognostic factors – gestational age <25 weeks at diagnosis, structural cardiac abnormality, chromosomal abnormality, polyhydramnios, contralateral lung-to-thoracic transverse area ratio <0.5, contralateral lung-to-head circumference ratio <0.62, left ventricular hypoplasia

### Pentalogy of Cantrell

- A rare defect resulting from a severe mesodermal fusion failure
- Comprises – diaphragmatic hernia (retrosternal defect), lower sternal defect, pericardial defect, major cardiac anomaly and epigastric exomphalos

### Differential diagnosis

- Congenital cystic adenomatoid malformation
- Lung sequestration
- Cystic lesions (bronchogenic, thymic, neuroenteric, duplication)
- Diaphragm eventration

### Postnatal diagnosis

- Absence of visible diaphragm
- Bowel loops seen in the chest
- Tip of nasogastric tube in the chest (only if stomach herniated)
- Paucity of bowel loops within abdomen
- Contralateral mediastinal shift
- Small contralateral lung

### Resuscitation at birth

- Avoid bag and mask positive-pressure ventilation (minimize visceral distension)
- Prompt endotracheal intubation in the delivery room for respiratory distress
- Replogle or wide-bore nasogastric tube insertion (will need to be passed beyond the usual distance)
- Chest radiograph to confirm diagnosis, nasogastric tube position and exclude other diagnoses

(congenital cystic adenomatoid malformation, pulmonary sequestration)

- Occasional fluoroscopy (eventration) or cross-sectional imaging (congenital cystic adenomatoid malformation, pulmonary sequestration) to exclude differential diagnosis in difficult cases

## Medical management

- Minimal stimulation with consideration of paralysis
- Abnormal pulmonary vascular reactivity produces reduced lung perfusion, pulmonary hypertension, right-to-left shunting through the foramen ovale, ductus arteriosus and intrapulmonary vessels
- Surfactant used in some centres
- Maintain preductal oxygen saturations at 85–90%
- Minimal ventilation pressures to reduce barotrauma. Iatrogenic injury from ventilation strategies may be significant and should be minimized
- Volume resuscitation and vasopressors (dopamine and dobutamine) often required
- Pulmonary vasodilatation with inhaled nitric oxide
- High-frequency oscillatory ventilation may be considered when conventional ventilation fails to correct hypoxia and hypercapnia, or when peak airway pressures remain high ( $>30$  cmH<sub>2</sub>O)
- Extracorporeal membrane oxygenation has not offered consistent results, but is used in some centres as rescue therapy
- Persistent pulmonary hypertension of the newborn is a major determinant of survival and consideration of the timing of surgery

## Surgical management

- Stabilization with medical treatment takes priority
- Surgical repair includes reduction of the herniated viscera into the abdominal cavity
- Closure of the diaphragmatic defect: direct suture  $\pm$  a prosthetic patch
- Diaphragm agenesis may require more extensive surgical intervention

## Complications

- Continued medical management of pulmonary hypoplasia
- Thoracic wall deformities with growth
- Detachment of prosthetic patch: may require further surgery

### 12.1 Eventration of the diaphragm

- Abnormal elevation of an otherwise intact diaphragm
- Similar to congenital diaphragmatic hernias, eventration of the diaphragm is more common on the left
- Paralysis of the diaphragm due to phrenic nerve palsy or traumatic/iatrogenic phrenic nerve damage
- Presentation is more often less dramatic and later than for those with congenital diaphragmatic hernia. Due to the limited respiratory reserve, poor feeding or sucking, associated with tiring, is

common

- Failure to thrive may be the presenting complaint due to poor feeding. Vomiting may be the presenting complaint
- Failure to recover from a lower respiratory tract infection or recurrent infections may prompt a chest radiograph which brings the diagnosis to light
- Fluoroscopy is diagnostic in most cases. Paradoxical movement of the affected diaphragm is seen during screening
- Surgical correction is via a thoracotomy, thoracoscopy or laparotomy depending on preference
- Patient who are asymptomatic or patients who improve without intervention may be treated conservatively

## 13. MALFORMATIONS OF THE AIRWAY AND LUNGS

### 13.1 Choanal atresia

- Obstruction at the level of the posterior border of the nasal septum – 90% bony, 10% membranous
- Incidence of 1 in 10 000
- Symptoms from birth (if bilateral) as neonates are obligate nose breathers
- Failure to pass a catheter beyond the posterior nares
- Transnasal surgical correction with postoperative temporary stenting

### Macroglossia

- Localized – haemangioma, lymphangioma
- Generalized – hypothyroidism, Beckwith–Wiedemann syndrome (check blood glucose)
- May require surgical reduction

### 13.2 Laryngeal cleft

- Incomplete separation of foregut into trachea and oesophagus
- Rare condition, may occur in isolation, involves larynx  $\pm$  trachea
- Associated with – OA/TOF, cardiac, palate, genitourinary anomalies
- Feeding aspiration, recurrent pneumonia, stridor, weak cry
- May require intubation  $\pm$  tracheostomy
- Endoscopic assessment
- Surgical repair may be complex

### 13.3 Congenital lobar emphysema (overinflation)

- Overexpansion of alveolar spaces – segment or lobe (normal lung histology)
- Cartilaginous deficiency/abnormality (35–50%)

- Post-infective alveolar septal fibrosis (30%)
- Extrinsic compression – cardiomegaly from congenital cardiac anomalies in 15% (ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot), aneurysmal dilatation of major vessels, bronchogenic cyst
- Acquired – preterm or small for gestational age neonates after long-term ventilation
- Inspiratory airflow – producing a ‘ball-valve’ defect, air trapping and compression of adjacent lung

## **Presentation**

- Some diagnosed antenatally on ultrasound
- Usually within a few hours of birth (50%) with severe respiratory distress
- Chest asymmetry, hyperresonant
- May be asymptomatic at birth, with symptoms by 6 months

## **Radiology**

- Left upper lobe (42%), right upper lobe (21%), right mid-lobe (35%), rare in lower lobes
- Hyperlucent overexpanded lung
- Herniation of emphysematous segment/lung across midline (anterior to mediastinum)
- Mediastinal shift
- Compression/atelectasis of adjacent lung/lobes
- Depression of ipsilateral diaphragm
- Ventilation–perfusion scan may confirm absent perfusion/ventilation in severe cases

## **Management**

- Mild cases – conservative, regular review with chest radiograph
- Echocardiogram
- Most require lobectomy – may be required urgently for life-threatening respiratory insufficiency. Emphysematous lobe may bulge out of the surgical field

## **Follow-up**

- After lobectomy, no significant functional impairment
- Asymptomatic overdistended lobes do not impair development of normal lung

## **13.4 Congenital cystic adenomatoid malformation**

- May be identified on antenatal ultrasound – echogenic fetal chest mass ± hydrops
- Some demonstrate resolution after birth (uncertainty regarding pathology/prognosis)
- 20–25% are stillborn or die rapidly from severe respiratory insufficiency
- Neonatal period – progressive respiratory distress (enlarging lesion with air-trapping)
- May require emergency surgery



- Symptoms are also related to degree of pulmonary hypoplasia (ipsilateral and contralateral), from compression
- Single lobe in 80%
- Displacement of cardiac apex
- Hyperresonant hemithorax

## **Radiology**

- Chest and abdominal radiograph will help to distinguish between a congenital cystic adenomatoid malformation and diaphragmatic hernia (demonstrate normal intestinal gas pattern in the former but not the latter)
- Early plain films may be radio-opaque (delayed clearance of lung fluid)
- Air-filled cystic spaces, adjacent lung compression, subtle changes (appear normal)
- Computed tomography (CT) scan – precise anatomical location and extent of disease (see below)

## **Management**

- Most will be sufficiently stable for complete preoperative assessment (radiographs and CT)
- Symptomatic – elective lobectomy
- Asymptomatic – controversial

## **13.5 Pulmonary sequestration**

- Congenitally abnormal non-functioning lung tissue
- No communication with the tracheo-bronchial tree
- Systemic blood supply from the aorta
- Large systemic blood supply can cause high-output cardiac failure

### **Intralobar pulmonary sequestration**

Sequestered lobe is contained within normal lobe. Asymptomatic or recurrent pulmonary sepsis, often in older children. Venous drainage to the pulmonary system, occasionally to the azygous/hemia-zygous.

### **Extralobar pulmonary sequestration**

Sequestered lobe has a separate pleural covering. Most common in left lower lobe, often seen on antenatal ultrasound. Associated with left-sided congenital diaphragmatic hernia (60%). Also seen with cardiac anomalies, pericardial defect, pectus excavatum, bronchogenic cysts, vertebral anomalies. May occur below the diaphragm.

## **Radiology**

- Require CT or magnetic resonance imaging (MRI) to identify/locate abnormal arterial supply

## Management

- Thoracotomy and resection, taking care with identification of blood supply (which is often large)
- Surgery advocated for risk – infection, malignancy
- Outcome is related to associated anomalies

## 13.6 Bronchogenic cyst

Abnormal bronchial budding. Rarely have any communication with the tracheobronchial tree. Some show early respiratory distress, recurrent pneumonia; confirm diagnosis on CT. Treatment is by surgical resection (there is a late risk of sarcomatous change).

## 14. NEONATAL TUMOURS

- 50% are diagnosed at delivery; a further 30% are diagnosed within a week of birth
- A palpable mass is the most common presentation
- Malignant tumours are rare, occurring 1 in 27 000 births
- Most solid tumours are benign
- Teratoma is the most common neoplasm (45% of all tumours)
- Neuroblastoma is the most common malignant tumour (15–25%)

### 14.1 Teratoma

- Embryonal neoplasm derived from the germ layers (ectoderm, mesoderm, endoderm)
- Most common in paraxial or midline location – sacrococcygeal (45–64%), mediastinal (10%), gonadal (10–35%), retroperitoneal (5%), cervical (5%), presacral (5%)
- Solid, cystic or mixed
- 80% benign, 20% malignant

### 14.2 Sacrococcygeal teratoma

- Incidence of 1 in 20 000 to 40 000 live births
- 75% female, 25% male
- Associated anomalies (18%)

## Diagnosis

- Antenatal – ultrasound imaging, elevated serum  $\alpha$ -fetoprotein/human  $\beta$ -chorionic gonadotrophin

(see below)

- Poor prognosis – polyhydramnios, placentomegaly, gestational age <30 weeks
- Late presentation – features of urinary or intestinal obstruction, lower limb neurology or malignancy
- Imaging – plain radiograph, MRI, CT

## **$\alpha$ -Fetoprotein**

Normally produced by the fetal liver, also by yolk sac tumour elements. Plot serum levels against a nomogram (levels fall rapidly following birth). Levels should fall to normal following successful resection. Elevated levels may suggest malignancy. Rising levels indicate recurrence.

## **$\beta$ -Subunit human chorionic gonadotrophin**

From chorionic syncytiotrophoblastic cells (malignant teratoma). Rising levels after surgery suggest persistent or recurrent tumour.

## **Complications**

- Placentomegaly
- Hydrops
- Cardiac failure
- Malpresentation, premature rupture of membranes, cord prolapse, placental abruption, shoulder dystocia
- Massive bleeding

## **Surgery**

- Resection (<2 months at latest) – may require combined abdominal and perineal approach. Technically difficult. Requires excision of coccyx
- Follow-up with 3-monthly tumour markers, clinical assessment (PR [rectal examination])  $\pm$  further imaging
- Greatest risk of malignant change – surgery after 2 months, incomplete excision, immature elements on histology

## **15. SPINA BIFIDA**

- Defects in the fusion of the neural tube, incidence of 1 in 500 to 1 in 2000 live births
- Defects of increasing severity – spina bifida occulta, meningocele, myelomeningocele, myelocele

## **Presentation**

- Less severe defects may not be apparent at birth, cutaneous stigmata (pigmentation anomalies,

excess hair, lipoma, dermal sinus)

- Obvious open lesion – skin defect, cord may be protected by pia arachnoid, or there may be an open neural tube defect (exposed neural plate)
- Many are associated with central nervous system abnormalities (hydrocephalus)

## **Assessment**

- Level of lesion (cervical, thoracic, lumbar, sacral – most will be lumbosacral), and size
- Neurological deficit – motor and sensory level, spontaneous limb movement, posture. Always begin sensory assessment from ‘abnormal to normal’ area
- Bladder/bowel function – appearance and sensation of perineum; rectal prolapse, absent natal cleft (paralysis of pelvic floor/sphincters)
- Hydrocephalus – bulging anterior fontanelle, persistent metopic suture, suture diastasis, setting-sun eyes, frontal bossing, enlarging head circumference (crossing percentile curves) ± Arnold–Chiari malformation (see below)
- Orthopaedic deformities – spine (kyphoscoliosis), hips (congenital dislocation), feet (talipes)
- Other abnormalities – sacral agenesis (partial/complete), cord tethering, renal tract anomalies (hypospadias, horseshoe kidney, exstrophy), congenital heart disease, anorectal malformation, craniofacial anomalies

## **Neurology level**

- **L3** – legs totally paralysed
- **L4/L5** – flexed hip, extended knee, no other movement
- **S1** – movement of the hip and knee, foot can dorsiflex but not plantarflex
- **S2/S3** – normal leg movements, still doubly incontinent

## **Immediate management**

- Prone positioning (with attention to prevent faecal soiling of exposed neural tissue)
- Cover exposed neural tissue with Clingfilm (wrapped around trunk)
- Broad-spectrum antibiotics
- Intermittent urinary catheterization

## **Surgery**

- Formal closure of defect with reconstruction of anatomical layers
- Ventricular shunt for hydrocephalus
- Delayed orthopaedic procedures may be required
- Clean intermittent catheterization ± bladder augmentation procedures in later life

## **Outcome**

Poor prognosis with severe hydrocephalus, severe kyphosis, thoracolumbar lesions, associated

malformations, poor social support:

- Meningitis and ventriculitis (10–15%) requires prompt treatment
- Hydrocephalus – thoracolumbar lesion (95%), lumbosacral (60%)
- Ambulation – dependent on level of lesion, orthopaedic abnormalities, intellect. Thoracic and lumbar (few achieve independence), sacral (most), lumbosacral (many can walk with callipers but may choose a wheelchair for ease)
- Lumbosacral: with clean intermittent catheterization, nearly 90% remain continent
- Intellectual development: dependent on level, up to 40% have IQ impairment

## 16. MISCELLANEOUS CONDITIONS

### 16.1 Antenatal torsion

#### Presentation

- Non-tender, discoloured scrotal swelling, usually unilateral
- Differential diagnosis – hydrocele, traumatic haematoma (breech delivery), incarcerated inguinal hernia (associated with a thickened cord), lesion secondary to patent processus vaginalis (meconium, intraperitoneal bleeding) infection, gonadal neoplasm

#### Investigations

- Abdominal radiograph may be helpful – identification of scrotal contents via patent processus vaginalis (air within a herniated bowel loop), meconium (antenatal intestinal perforation)
- Ultrasound – distinguish solid from cystic masses. Useful if concerned about a possible tumour

#### Management

- Testis is considered non-viable at the time of presentation
- Many surgeons will not remove ischaemic testis but will elect for early fixation of the contralateral side

### 16.2 Accessory digit

- Extra digits (polydactyly) may be simple or complex
- Tags or digit remnants – most common, near metacarpophalangeal joint of little finger
- No palpable bone in base, attached by a soft tissue stalk (containing digital nerve and vessels)
- Requires surgical excision to prevent formation of a painful neuroma
- More complex anatomy requires orthopaedic referral for formal amputation

---

# General paediatric surgery

---

## 17. HEAD AND NECK SURGERY

### 17.1 Ranula

- A mucus retention cyst of the sublingual salivary gland caused by partial obstruction of the duct
- Presents clinically as soft, occasionally tense, clear swelling on the floor of the mouth
- Can increase in size after first appearing
- Usually symptomless, although they can be painful
- Treatment consists of marsupialization of the cyst by incising the cyst wall and suturing the edges open; thereby draining the obstructed gland. Only very occasionally is excision required

### 17.2 Lymphatic malformation (cystic hygroma, lymphangioma)

- Is a congenital anomaly caused by the failure of connection of part of the lymphatic system during embryological development
- Lymphangioma is a misnomer, because this is not a tumour associated with cell turnover or proliferation
- A lymphatic malformation (LM) in the head and neck is called a cystic hygroma
- Location is the only distinguishing feature from LMs in other sites
- Present at birth but not always obvious in the neonatal period, and the presentation is often precipitated by an unrelated infection (e.g. viral upper respiratory tract infection)
- Most common sites of occurrence in order of frequency are:
  - Neck
  - Axilla
  - Chest
  - Abdominal
- Can be identified antenatally
- Present clinically as a brilliantly transilluminable multicystic swelling
- Usually soft
- If infected they can become tense, red and painful; occasionally progressing to abscess formation
- Can also cause symptoms by exerting pressure on adjacent structures (e.g. dysphagia, stridor, respiratory compromise)

## Differential diagnosis

- Includes haemangiomas, lipomas, dermoid cysts and mixed lesions. Lymphangiomas are rarely of a 'pure' pathology; commonly they are combined with vascular or fatty elements
- Ultrasound used to confirm the diagnosis and assist with identification of macrocystic and microcystic varieties
- Occasionally a CT scan is required to define extent large lesion and anatomic relationships

## Treatment options

- Conservative management has become the aim – commonly after initial presentation and increase in size these lesions undergo involution; this is also common after infection
- Sclerotherapy – the most common agent is OK-432, which is a *Streptococcus*-derived antigen. It is more successful in predominantly macrocystic lesions. Causes an acute inflammatory reaction (with acute swelling and symptoms) that causes involution but may have an adverse, temporary effect on contiguous structures (e.g. stridor)
- Surgical excision is sometimes required for larger lesions or those that do not respond to other modalities of treatment

## 17.3 Thyroglossal cyst

- Thyroid gland develops as a diverticulum at the foramen caecum and descends to its cervical location in fetal life. Path is marked by the thyroglossal tract. Persistence of part or the entire tract leads to thyroglossal duct and cyst
- Presents as a midline swelling between the tongue and infra-hyoid region. Moves with swallowing and protrusion of the tongue, although this sign is relatively insensitive
- Ultrasound is indicated to identify a normal thyroid gland, and to confirm the diagnosis
- Surgical excision includes excision of the cyst, along with the tract (and central portion of the hyoid bone), all the way to the base of the tongue

## 17.4 Preauricular pits

- Ectodermal inclusions that occur during formation of the auricles of the ear
- Shallow, blind-ending pits which end in the subcutaneous tissues
- Present at birth and often bilateral
- Can become infected and surgical excision is sometimes recommended

## 17.5 Branchial arch remnants

- In weeks 4–8 of fetal life the cervicofacial region is occupied by four branchial arches with corresponding pharyngeal pouches with intervening clefts. Persistence or abnormal development

leads to branchial fistulas, sinuses and cysts (least common)

- First, third and fourth branchial anomalies are all rare
- Second branchial arch fistulas and sinuses are common and are found along the anterior border of the sternocleidomastoid, usually at the junction of the middle and lower thirds. The tract ascends between the bifurcation of the carotid artery to the tonsillar fossa

## 17.6 Cervical lymphadenopathy

- Most common cause of neck swelling over 2 years of age
- Usually ascribed to viral infection but can also be secondary to bacterial infections in and around the head and neck
- Nodes of the anterior cervical chain are more commonly affected
- Enlargement is usually self-limiting
- In toxic children, intravenous antibiotics may be required. Penicillin and flucloxacillin are used to cover staphylococcal and streptococcal infections
- If the infection is not well contained, suppuration and abscess formation supervene. The node is then tender and fluctuant with overlying redness of the skin. Ultrasound is useful in identifying pus in the centre if there is uncertainty. Incision and drainage are required
- Enlarged lymph nodes may be the result of tuberculous or atypical mycobacterial infection
- Cat scratch disease can also present with chronic enlargement. There may not be a memory of the implicating scratch, which precedes the lymphadenopathy by 3–4 weeks
- Lymphoma may present with enlarged lymph nodes. Abnormal nodes and those that persist for more than 3 months (without an obvious cause) should be biopsied

## 17.7 Haemangiomas and vascular malformations

- Haemangiomas are vascular tumours that exhibit endothelial hyperplasia (defined by the suffix – angioma)
- Present in 2% of newborns; the incidence increases to 10% at 5 years
- Several growth factors are thought to be involved in pathogenesis; lead to proliferation of the vascular tissues in the first months of life, with an increase in the size of the lesion
- Many subsequently regress spontaneously
- Arteriovenous malformations are always present at birth but may not be evident. Unlike haemangiomas they have no propensity for regression
- A bruit may be evident
- Visible lesions may be disfiguring
- Complications – ulceration, infection, necrosis, bleeding
- Haemolysis and activation of the coagulative system may occur with large lesions
- Symptoms particular to location may occur (gastrointestinal/pulmonary bleeding, obstruction)
- High-output cardiac failure may occur with large arteriovenous malformations that cause a significant steal

## Investigations



- Usually include an ultrasound to confirm the diagnosis and extent of the lesion, with Doppler assessment of flow characteristics
- MR or CT scans may be required for lesions in some sites
- Angiography may assist in the anatomical definition of arteriovenous malformations

## **Treatment**

### **Haemangiomas**

- Conservative management is the mainstay of management of asymptomatic haemangiomas; vascular malformations that cause no symptoms can also be treated conservatively
- Compression therapy – can be used for accessible lesions and may accelerate involution of haemangiomas
- Laser therapy – used for some superficial lesions that are disfiguring
- Embolization/sclerotherapy – used for symptomatic lesions' multiple treatments may be required
- Interferon- $\alpha$  – shown by some series to be of benefit in haemangiomas that are resistant to other modalities of treatment. Treatment is required over a few months. Chemotherapy (vincristine, cyclophosphamide) is sometimes used
- Propranolol, the newest treatment option in the management of haemangiomas. It seems particularly useful in haemangiomas in and around the airway, where it may be the first-line management in those requiring treatment, and replace complicated surgery
- Surgical excision – used for lesions that give rise to complications and do not respond to conservative or other modalities of treatment

### **Vascular malformations**

- Sclerotherapy (as for lymphatic malformation – see above)
- Embolization of large feeding vessels
- Surgical excision

## **17.8 Central venous access**

- Surgical implantation of a venous access device into a central vein
- Venous access device can be either of an externally accessible line (e.g. Hickman – no need for skin penetration and therefore more applicable in younger more needle phobic patient) or implantable (subcutaneous) type (portacath – less likely to dislodge, lower infection rate)
- The central veins most commonly used for access in decreasing order of frequency are:
  - Internal jugular
  - External jugular
  - Subclavian
  - Femoral
  - Other (e.g. azygous)

## **Indication**

- Need for long-term central access for intravenous nutrition (intestinal failure)
- Central venous access for chemotherapy (oncology/haematology)
- Long-term access for antibiotics or long-term intravenous therapy (e.g. cystic fibrosis, inborn errors of metabolism, osteogenesis imperfecta)
- Need for repeated blood sampling in monitoring or managing disease

## Procedure

- Can be percutaneous or open
- Percutaneous ultrasound-guided access to vein using a Seldinger technique to insert catheter (*advantages*: less invasive, less trauma to vein, can re-use veins more often; *disadvantages*: need for ultrasonography, unsuitable for deeper veins)
- Open cut-down on to vein with direct insertion into vein of choice (*advantages*: direct visualization of vein, can be used in smaller children; *disadvantages*: trauma to veins, possibly higher infection rate)

## Complications

- Dislodgement
- Line infection
- Bleeding/haemothorax
- Pneumothorax
- Leakage or line breaking
- Blockage
- Thrombosis (in line or vein itself)
- Migration, with cardiac effects (ectopics) if distal migration or access failure if proximal migration  
Cardiac tamponade

## 18. THORACIC SURGERY

### 18.1 Congenital malformations

- Some congenital lesions that are not detected in the antenatal period, and that do not cause symptoms in the neonatal period, can present in childhood. They often present with recurrent chest infections and coughing
- **Congenital diaphragmatic hernia** (see [Section 12](#)) – may remain undetected until a chest infection supervenes and is detected on chest radiograph. This is especially true for anterior hernias (of Morgagni)
- **Eventration of the diaphragm** – defined as elevation of the hemidiaphragm that results from paucity of muscle in the absence of a defect. The differential diagnosis is a phrenic nerve palsy. Eventration can sometimes present in infancy and childhood as repeated chest infections or failure to recover from a relatively minor chest infection, or an accidental finding
- **Pulmonary sequestrations, congenital cystic adenomatoid malformation and congenital lobar**

**cysts** – may present outside the neonatal period, although they are increasingly being diagnosed antenatally. Symptomatic lesions are surgically treated after resolution of any acute complications

## 18.2 Chest wall deformities

### **Pectus excavatum and pectus carinatum**

- Pectus excavatum (funnel chest) is more common than pectus carinatum (pigeon chest). Both are three times more common in boys compared with girls
- Aetiology of these conditions is unknown. Some form of growth disturbance in the costochondral junction is thought to exist, giving rise to depression (excavatum) or protrusion (carinatum) of the sternum
- Associated with congenital abdominal wall defects (congenital diaphragmatic hernia)
- Can be asymmetrical or unilateral
- Family history in some index cases
- Pectus excavatum can be seen in connective tissue diseases such as Marfan and Ehlers–Danlos syndromes; a thorough physical examination for the stigmata of these should be carried out
- Majority of patients with pectus excavatum have some deformity from birth; only 30% of patients with pectus carinatum have any abnormality at birth
- Can be a worsening of the deformity during growth spurts such as puberty
- Most children present because they or their parents are concerned about their appearance. Sometimes this is severe enough to prevent older children and teenagers from participating in sports and other activities that cause embarrassment
- No significant effect of either condition on cardiorespiratory function. Although there was much speculation of decreased cardiorespiratory reserve in severely affected children, this has not been substantiated in studies
- Treatment:
  - Most cases can be managed by reassurance; muscle and breast development mitigate the appearance
  - Indication for surgical intervention should be critically scrutinized
  - Surgical correction has involved highly invasive procedures that resect the costal cartilages, invert the sternum with placement of metal rods or bars to correct the deformity
  - A minimally invasive approach is possible and has made surgeons reconsider the indications for surgery

### **Poland syndrome**

- Unknown aetiology
- Characterized by hypoplasia or aplasia of the pectoralis major muscle and one or more of the following: hypoplasia or aplasia of the breast or nipple, aplasia of ribs, or syndactyly/bradydactyly

### **Sternal clefts**

- Occur in isolation or associated with other syndromes, the most common being pentalogy of Cantrell (sternal cleft, omphalocele, pericardial and cardiac defects, and diaphragmatic hernia)

## 18.3 Oesophageal foreign bodies

- Children swallow a multitude of foreign bodies. Coins are the most common but the list includes pins, needles, hairclips and small toys. Most of these items traverse the gastrointestinal tract without any difficulties. Unwitnessed ingestion can come to light because of symptoms, including choking, coughing, vomiting and regurgitation
- If the object fails to get into the duodenum the likeliest site of impaction is at the level of cricopharyngeus, followed by the aortic and left main bronchus impressions on the oesophagus, the gastro-oesophageal junction and the pylorus
- If the development of symptoms prompts investigation, radio-opaque objects can be seen on radiograph
- In the absence of drooling, a period of observation while allowing fizzy drinks can be tried and patient reassessed over 4-6 h to see if it passes easily
- However, disc batteries cause chemical injury and should be removed immediately if stuck. If recognized as such on history or radiograph, should be expedited
- Chronic hair or fibre (e.g. carpet) ingestion has occasionally lead to trichobezoars that require laparotomy
- Rigid (more versatile) or flexible endoscopy is used for retrieval. Occasionally oesphagotomy is required for chronic or embedded lesions

## 18.4 Caustic ingestion

- Caustic damage can occur through ingestion of common household products by exploring toddlers
- Alkali ingestion more commonly affects the oesophagus, whereas acid ingestion more often affects the stomach
- Oesophagus can be severely affected without any obvious injury
- Emergency management (National Poisons Unit):
  - ABCs (i.e. airway, breathing, circulation)
  - Steroids have been shown to have no benefit in trials
  - Endoscopy within the first 24 h to assess injury
- Patients can then be observed for symptoms of stricture formation and other complications including:
  - Perforation
  - Mediastinitis
  - Fistulae formation
- Caustic ingestion can therefore have devastating consequences. Major palliation or reconstructive surgery may be necessary

## 18.5 Parapneumonic effusions

- A transudate into the pleural space during the course of a pneumonic infection
- Empyema is defined as pus in the pleural space, an infected parapneumonic effusion
- Sometimes clinically difficult to distinguish between these two entities in the child who does not recover from pneumonia and has signs of an effusion. Continued pyrexia can be caused by the original disease in the former, or pleural pus in the latter. In either case culture of the fluid is usually negative
- Pressure effects of the fluid, pulmonary consolidation and thickening of the pleura can all limit chest expansion and deter recovery
- Ultrasound is helpful in defining the depth of the effusion, in identifying the presence of loculations and any pleural thickening, and in visualizing the presence of debris in the fluid to suggest pus
- Drainage is indicated by failure to resolve with adequate (albeit presumptive) antibiotic therapy. Tube thoracoscopy is usually coupled with suction (3–5 kPa)
- Fibrinolytic therapy with urokinase is used if ultrasound shows marked debris or loculations
- All patients require aggressive physiotherapy
- Chest tube is removed when drainage is  $\leq 50$  ml/day (usually on days 3–5)
- Video-assisted thoracoscopic surgery is an alternative to, or adjunct to, tube drainage alone. It allows drainage of the pleural space and breaking down of any loculations and decortication in advanced cases
- Surgery (including thoracotomy for decortication) is also required when the lung fails to re-expand after tube therapy, but has had a much diminished role since the advance of fibrinolytics
- Postoperative recovery can be assessed by the return of normal flow patterns on respiratory function tests in the outpatients

## 19. GASTROINTESTINAL SURGERY

### 19.1 Abdominal wall herniae

#### Umbilical herniae

- Umbilicus develops by closure of the cicatrix after the cord thromboses. The cicatrix closes by fibrosis, probably aided by abdominal wall muscle contraction. Complete closure can take until year 5 of age
- Herniae present as a bulge through a circular defect in the centre of the cicatrix
- Usually symptomless, but rarely a cause of abdominal pain
- Cosmetic concerns (or teasing) are the main indications for surgery
- Surgical correction consists of repair of the defect with strong mattress sutures. This may be delayed until after the fifth birthday

#### Supraumbilical hernia

- Less common than umbilical hernia
- Defect is sited above the cicatrix, therefore elliptical and points downwards
- Do not resolve and therefore require surgical closure

## **Epigastric hernia**

- Present as intermittent swellings usually midway between the umbilicus and the xiphisternum
- Although present from birth, usually present in school-age children, often when the child complains of incidental (non-related) abdominal pain (although mild pain can be caused by strangulation of fat in the defect, this is rare)
- The defect is often difficult to define
- Surgical correction is elective because these hernias are asymptomatic and cause no problems

## **Inguinal hernia**

- A congenital abnormality caused by persistence of the patent processus vaginalis, a peritoneal tube along the path of testicular descent into the scrotum
- Incidence in general population is 1–2%; 10 times more common in boys and in preterm infants
- Rare association of inguinal hernia in girls with complete androgen insensitivity syndrome; girls presenting with inguinal hernia should have their chromosomes checked
- Present as intermittent swellings in groin which may reach the scrotum
- 10–20% of boys have a metachronous hernia after index presentation
- Irreducibility for prolonged periods can lead to obstruction (abdominal pain, distension and vomiting) and eventually strangulation (hard, tender swelling)
- Elective repair advised
- Patients who present with an irreducible hernia require hernia reduction and delayed repair after the resultant oedema has settled; this generally involves a 24- to 48-h hospitalization and repair before discharge
- Repair consists of reduction of the contents of the hernia, and ligation of the patent processus through a groin incision or a laparoscopic repair

## **Hydroceles**

- Identical to inguinal hernia in aetiology
- Usually present as symptomless fluid-filled swellings of the scrotum that are transilluminable, and are variably reducible
- Occasionally present as tense swellings during an acute illness
- Unusual variety is a hydrocele confined to a portion of the cord only (encysted hydrocele)
- Most hydroceles (unlike hernias) resolve without surgery in the first few years of life. Surgery is indicated if they fail to resolve

## **19.2 Pyloric stenosis**

- A condition of unknown aetiology characterized by hypertrophy of the pyloric muscle, resulting in gastric outlet obstruction
- Occurs in 1 in 500–1000 live births, with a male:female ratio of 4:1
- Strong family history in some cases

- Presentation is that of repeated, progressive, non-bilious, often forceful (typically projectile) vomiting; most commonly in weeks 4–6 after birth:
  - Weight loss and dehydration common at presentation
  - Pathognomonic sign is a palpable tumour (olive) in the right upper quadrant
  - May be visible peristalsis
- Ultrasound to confirm the diagnosis only if a mass is not palpable:
  - Dimensions positive for pyloric stenosis – wall thickness >4 mm, length >17 mm and diameter >15 mm (younger or preterm infants may have smaller measurements)
- Vomiting of stomach contents with gastric acid leads to a hypokalaemic, hypochloraemic, metabolic alkalosis
- Paradoxical aciduria in late stages
- Preoperative preparation is aimed at correcting these abnormalities:
  - Acute administration of 0.9% saline (10–20 ml/kg) is used for resuscitation
  - Fluid is prescribed at 150 ml/kg per day of 0.45% saline with KCl
  - When plasma bicarbonate is <25 mmol/l, correction is adequate, and anaesthesia is safe
- Surgical correction can be performed through a right upper quadrant incision, a paraumbilical incision or laparoscopically
- The thickened muscle is divided along its entire length down to, but not breaching, the mucosa
- Postoperative feeds are generally given after 6–12 h and most patients are discharged within 24–48 h after surgery

## 19.3 Gastrostomy

- Temporary or permanent insertion of tube into stomach
- Gastrostomies can be either of a button type (e.g. MicKey or Mini) or tube types (e.g. MIC tube or percutaneous endoscopic gastrostomy – PEG)
- The method of fixation to the stomach can be of either a balloon (e.g. MicKey or Mini) or a flange (e.g. PEGs), or sutured to the stomach wall (Stamm)

Indications can be broadly divided into:

- Patients unable to have any oral intake due to anatomical or physiological abnormalities
- Patients requiring hyperalimentation of oral feeding to allow growth which cannot be expected to be achieved with oral intake only
- Patients requiring particularly unpalatable feed supplementation

The main types of procedures:

- PEG: the gastrostomy is inserted via stab incision in the abdominal wall under vision from the inside the stomach using an endoscope
- Button gastrostomy can either be primarily done laparoscopically or endoscopically
- A Stamm gastrostomy is a type of open gastrostomy in which a double purse-string suture on the stomach is used to fix the gastrostomy tube in place



# Complications

- Infection, granulation tissue
- Leakage
- Blockage
- Skin excoriation secondary to acid leakage
- Separation and intraperitoneal leakage with resulting peritonitis
- Unmasking of gastro-oesophageal reflux

## 19.4 Gastro-oesophageal reflux disease

- Gastro-oesophageal reflux (GOR) is defined as involuntary (passive) reflux of gastric contents into the oesophagus not caused by noxious stimuli. Gastro-oesophageal reflux disease (GORD) is defined as symptoms and complications arising from GOR
- GOR is present in many newborns, in whom it does not necessarily prepresent a clinical disease, but rather a somewhat delayed physiological development
- GORD is more common in neurologically impaired children and those with neuromuscular disease. Gastrointestinal anomalies associated with a high incidence are: oesophageal atresia, congenital diaphragmatic hernia and abdominal wall defects
- Vomiting is the most common symptom of GOR in an infant, and is usually non-bilious and effortless
- Apnoeas and bradycardias are frequent presenting features in neonates and infants. In some infants, these symptoms may progress to acute life-threatening events (ALTEs). ALTEs are acute respiratory events characterized by apnoeas, bradycardias and acute respiratory distress, and sometimes respiratory arrest
- Excessive vomiting can lead to failure to thrive. Haematemesis is an uncommon presenting feature, but may be present. Older children may be able to describe the typical heartburn associated with GORD. This retrosternal pain may be associated with a bitter taste in the mouth. Respiratory symptoms of wheezing and recurrent pneumonias are uncommon but recognized features
- Sandifer syndrome is a constellation of abnormal posture (especially back arching) due to muscular spasm involving the back and neck muscles associated with reflux

## Investigations

- Investigation consists of a combination of three main investigative tools (pH study, contrast study and upper GI endoscopy). The choice of first-line investigation is based on a combination of availability, expertise and symptoms
- A 24-h pH study is considered by most as the gold standard investigation. A multi-channel impedance study can be combined with the pH study, and may become the 'platinum standard' investigation
- Radio-isotope gastric emptying scan (milk scan) can be used to assess gastric emptying reflux aspiration
- Bronchoscopy and bronchoalveolar lavage is sometimes used to detect lipid-laden macrophages as evidence of aspiration from reflux in those with respiratory symptoms



- Oesophageal manometry studies may be indicated in those cases of reflux stricture that cannot be distinguished from achalasia

## **Treatment**

- Conservative management initially
- Feed thickening has been shown to reduce the clinical symptoms associated with GOR. Thickening agents such as alginate (Gaviscon) and pectin are gelling agents that can be added to milk feeds and result in a thickened feed that remains in the stomach easier than liquid feeds
- Pre-thickened milk feeds (e.g. Enfamil AR) contain an easy-to-digest rice starch that thickens in the stomach and is successful in helping reduce symptoms in some children
- Changes in posturing immediately postprandially have been shown to decrease GORD both clinically and experimentally. The upright position is optimal in the postprandial period
- Changes in feeding pattern can be used to achieve a regimen that minimizes symptoms. Smaller volumes and more frequent feeds may help
- Gastrointestinal prokinetics (e.g. domperidone and erythromycin) are used to promote gastric emptying, reduce episodes of GOR and improve symptoms
- Nasojejunal feeding is an alternative to surgical intervention

## **Indications for surgical intervention**

- ALTE
- Hiatus hernia (GORD will not resolve with medical management)
- Recurrent aspiration and pneumonias
- Stricture
- Failure of, or need for, continued maximum medical management (decreases the need for long-term medical management, particularly in neurologically normal children)
- Barrett oesophagus (relative indication)

## **Operation**

- Fundoplication for GORD aims to address/augment the main contributing factors preventing reflux and to reverse any pathology present
- Fundoplication involves wrapping the fundus of the stomach around the lower intra-abdominal oesophagus
- Doppler assessment can identify blood flow, or lack of it, in the bowel wall
- Air enema under radiological control is used to reduce the intussusceptions – with a success rate of around 85%; contraindicated if there are signs of perforation
- Surgical management is indicated for signs of peritonitis, perforation or a failed air enema

## **19.5 Intussusception**

- Telescoping of one part of the intestine into the other

- Peak incidence between 4 months and 1 year
- Most cases are 'idiopathic' ileocolic intussusception; enlarged Peyer patches are believed to be causative in most of these cases
- In 5–10% there is a pathological lead point – Meckel diverticulum, duplication cyst, polyp, haemangioma or a bleeding point in Henoch–Schönlein purpura; may present with recurrent intussusception
- A lymphomatous deposit in the bowel wall can act as a lead point
- Classic triad of symptoms (but not present in all patients):
  - Abdominal pain (and drawing up of legs)
  - Bleeding per rectum (red currant jelly stools)
  - Palpable mass
- Vomiting, constipation or diarrhoea may be present and may predate the occurrence of intussusception and cause diagnostic difficulty
- Complete obstruction may be present, but is usually late in the presentation
- Patients can present in extremis, with signs of shock and sepsis
- Management – careful attention to primary resuscitation and fluid management; this can be the most important aspect of management:
  - Children can need up to and beyond 40 ml/kg fluid resuscitation
  - Triple antibiotics should be started when the diagnosis is suspected
  - Nasogastric decompression required if there are signs of obstruction
  - Plain abdominal film may reveal signs of established obstruction and a soft tissue mass may be seen
- Ultrasound scan confirms diagnosis, with the appearance of the typical target lesion of the telescoping bowel

## 19.6 Appendicitis

- Acute appendicitis is one of the most common paediatric surgical emergencies
- Incidence increases with increasing age, but sometimes seen in children aged as young as 2 years
- Presentation in the younger child can be atypical and the diagnosis difficult, resulting in later presentation in these children, with a higher proportion presenting with complicated appendicitis (mass or abscess formation)
- Typical history is of colicky central abdominal pain shifting to right iliac fossa, followed by vomiting that is usually non-bilious
- Characterized by low-grade fever and mild tachycardia; may be fetor
- Localized tenderness in the right iliac fossa; localized percussion tenderness may also be present
- Advanced cases may be septic, with hypovolaemia and marked fever
- May be overt peritonitis to suggest perforation
- History in atypical cases may mimic urinary tract infection, with dysuria, frequency and fever
- Diarrhoea may be the prominent symptom, especially with a pelvic appendix

## Differential diagnoses

- Urinary tract infection

- Gastroenteritis
- Mesenteric adenitis
- Ovarian pathology (Mittelschmerz, ruptured follicular cyst)
- Pancreatitis
- Meckel diverticulitis
- Viral illness
- Respiratory tract infection
- Diabetic ketoacidosis

## Investigations

- Urinalysis to rule out urinary tract infection – urgent microscopy if urinalysis is positive, as a pelvic appendix can give rise to white cells in the urine
- In straightforward cases no other investigation required. Raised white blood cells and elevated C-reactive protein are often present, but are not specific or sensitive
- Ultrasound scan can confirm the diagnosis in some cases that are not clear cut. Particularly useful in the pubertal female. The typical finding is a dilated, non-compressible appendix. There may be some free fluid in the right iliac fossa. However, a negative ultrasound scan does not rule out appendicitis
- Repeated examination and careful observation are the most useful tools in doubtful cases

## Management

- Appendicectomy should be performed as soon as possible – by traditional right iliac fossa incision or laparoscopically
- One dose of preoperative antibiotics is given; the postoperative antibiotic regimen will be dictated by the surgical findings

## 19.7 Meckel diverticulum

- A congenital remnant of the vitellointestinal duct, which is a connection between the embryonic gastrointestinal tract and the yolk sac; persistence of part of this tract results in a vitellointestinal band, cyst, tract or a Meckel diverticulum
- Meckel diverticulum contains all layers of the abdominal wall, and often contains ectopic gastric or pancreatic mucosa
- Classically found 60 cm from the ileocaecal valve, is 5 cm long and has an incidence of 2% in the general population
- Clinical presentation depends on resulting complications:
  - Intussusception can occur with the diverticulum acting as the lead point
  - Bleeding can occur as a result of ulceration secondary to acid secretion in the ectopic gastric mucosa. Melaena results, with fresh blood per rectum in cases with massive bleeding. Haematemesis is sometimes present
  - Meckel diverticulitis with/without perforation results from inflammation of the mucosa. Signs and symptoms can often mimic appendicitis

- Intestinal obstruction can result from volvulus around the vitellointestinal band, herniation of small bowel beneath the band or intussusception
- May be an incidental finding
- Investigations are dictated by the clinical presentation, and can include full blood count, clotting screen and an abdominal ultrasound which can sometimes identify a Meckel diverticulum or cysts. A Meckel scan (using  $^{99m}\text{Tc}$ ) relies on the uptake in ectopic gastric mucosa, but gives a false-negative result in up to 25% of patients
- Laparoscopy is sometimes required as an investigative tool
- Treatment consists of resection of the diverticulum
- Treatment of incidentally found lesions is debated; some advocate excision

## 19.8 Undescended testis

- Defined as undescended if it is not able to be brought down into the scrotum; divided into palpable and non-palpable
- **Ectopic testis** – one that is palpable but located outside the line of normal descent (superficial inguinal pouch, perineum)
- **Retractile testis** – one that can be manipulated into the scrotum and remains there, albeit briefly; these require no surgical intervention
- Incidence of retractile testis at birth varies with gestational age:
  - At term the incidence is 2–5%; at 30 weeks' gestation it is 20–50%
- Testicular descent can occur after birth
- Overall incidence is 1% at 1 year of age. Thereafter descent is unlikely to occur. As a result of the inherent risks (torsion, trauma, tumour and impaired spermatogenesis) undescended testes are fixed in the scrotum
- If testis is palpable, the inguinal canal is explored and the testis placed in the scrotum
- Boys with non-palpable testis undergo laparoscopy in an attempt to locate the testis. Occasionally the operation is performed in two stages

## 19.9 Testicular torsion

- Testicular torsion is a surgical emergency
- Presentation is with acute testicular pain – may be referred to the groin or abdomen
- There is usually some swelling at presentation; a secondary hydrocele may be present. The hemiscrotum may be erythematous in advanced cases. On examination the testis is swollen and tender
- Differential diagnosis and key points:
  - Epididymo-orchitis – difficult to differentiate, may have positive urinalysis
  - Torsion of hydatid of Morgagni – may be difficult to differentiate; localized tenderness with blue dot sign on superior pole
  - Acute enlargement of a hydrocele – unable to feel testis through fluid; may have an intercurrent viral illness

- Idiopathic scrotal oedema – erythema and oedema affecting the skin of the scrotum (often bilateral), which extend on to the perineum and inguinal region; testes are non-tender, otherwise the diagnosis is not entertained
- Investigations:
  - Urinalysis and/or midstream urine should be performed to rule out infection
  - Doppler ultrasound of the testis is sometimes obtained, but is seldom helpful in doubtful cases; the torsion may also be intermittent. Awaiting non-helpful ultrasonography can delay intervention
- Emergency surgical exploration is required to confirm the diagnosis and save the testis

## 19.10 Phimosis

- Defined as narrowing of the preputial ring that prevents retraction of the foreskin. At birth the foreskin is usually non-retractile (physiological); this regresses with age
- Percentage of boys with retractile foreskin by age: newborn infants, 4%; 1-year-old boys, 50%; 4-year-old boys, 90%
- Voiding with ballooning of the prepuce is the most common reason for referral, but is a normal occurrence with physiological phimosis
- Recurrent mild ammoniacal irritation of the tip of the foreskin may also occur, but responds to simple hygienic care
- Physiological phimosis is not an indication for circumcision
- Pathological phimosis is most commonly the result of balanitis xerotica obliterans. In this condition, equivalent to lichen sclerosis atrophicus, the foreskin is thickened, inflamed, scarred and unyielding. Often a sclerotic thickened white scar replaces the supple foreskin. Circumcision is performed in these cases
- Associated or eventual urethral meatal stenosis must be looked for in these boys
- Pathological phimosis may rarely be secondary to repeated attacks of infection that cause scarring
- Usual infecting organism is *Staphylococcus sp.* – Flucloxacillin or co-amoxiclav is usually therapeutic
- Chronic inflammation may lead to a rigid, fibrous foreskin

## 19.11 Hypospadias

- Hypospadias is an abnormality in which the urethral meatus is situated proximal to the tip of the penis on its ventral aspect
- Anatomically it is described by the position on the meatus as:
  - Glanular
  - Coronal
  - Penile
  - Penoscrotal
  - Perineal
- Along with the abnormality of the position of the meatus there is often a degree of deficient ventral development, resulting in curvature of the penis (chordee)
- A hooded foreskin is also evidence of a ventral deficiency in penile development

- Incidence is around 1:300 live births
- Aetiology unknown in most cases – seen in conditions associated with deficient testosterone secretion or responsiveness (disorders of sexual differentiation)
- Hypospadias with undescended testis should be investigated as potential cases of disorders of sexual differentiation
- Severe forms of hypospadias (e.g. penoscrotal and perineal) are associated with renal tract (and occasionally other systems) anomalies
- Surgical correction includes correction of any chordee, tubularization of appropriate tissue to create a new urethra and skin cover. Tissues used to create the urethra include:
  - Native urethral plate
  - Preputial skin (hence circumcision is contraindicated in patients with hypospadias)
  - Buccal or bladder mucosa
- Postoperative complications include infection, wound dehiscence, meatal stenosis and fistula formation

## 20. FURTHER READING

Arensman R, Bambini DA, Almond PS (2000). *Pediatric Surgery (Vademecum)*. Georgetown, TX: Landes Bioscience.

Ashcraft KW (2000). *Pediatric Surgery*, 3rd edn. Philadelphia: WB Saunders Co.

Burge DM, Griffiths DM, Steinbrecher HA, Wheeler RA (2005). *Paediatric Surgery*, 2nd edn. London: Edward Arnold Ltd.

Coran A, Pierro A, Geiger J, Spitz L (2007)

*Operative Pediatric Surgery*, 6th edn. London: Hodder Arnold.

Hutson JM (1988). *The Surgical Examination of Children*. Oxford: Butterworth-Heinemann Ltd.

Nakayama DK et al. (1997). *Critical Care of the Surgical Newborn*. Oxford: Blackwell.

Stringer M, Oldham K, Moriquand P, Edward H (2006). *Paediatric Surgery and Urology: Long term outcomes*. 2nd edn. Cambridge: Cambridge University Press.

# Picture Permissions

---

The publisher would like to acknowledge the following image sources:

## **Emergency Paediatrics**

The following figures are reproduced from the BMJ Books publication *Advanced Paediatric Life Support: The Practical Approach 4th edition*, The Advanced Life Support Group, 2004.

*Infant choking protocol*, page 156

*Pathophysiology of drowning*, page 170

## **Hepatology**

The following figures are reproduced from BC Decker publication *Paediatric Gastrointestinal Disease 4th edition*, Walker, W. Allen *et al.*, 2004.

*The two models of hepatic organization*, page 343

*The three variants of biliary atresia*, page 351

## **Nephrology**

The following figures are reproduced from the Blackwell publication *The British Journal of Urology*, Vol 81, supplement 2, April 1988, pp. 33–38.

*Creatinine clearance in the human fetus and newborn infant*, page 529

*Fractional sodium excretion in the human fetus and newborn infant*, page 530

The following figure is reproduced from the Blackwell publication *Clinical Paediatric Physiology*, Godfrey, S., Baum, J.D., 1979.

*Tubular function*, page 532

The following figure is reproduced from the Lippincott Williams and Wilkins publication *Pediatric Nephrology 3rd edition*, Holliday, M.A., Barrat T.M., Avner D.E., 1994.

*Renal tubular acidosis*, page 546

The following figure is reproduced from the American Society of Pediatrics publication *Pediatrics*, Vol 67, page 396, 1981.

**Every effort has been made to contact holders of copyright to obtain permissions to reproduce copyright material. However, if any have been inadvertently overlooked, the publisher will be pleased to make the necessary arrangements at the first opportunity.**



abacavir [ref 1](#)  
ABCDE approach [ref 1](#)  
abdominal pain [ref 1](#)  
    functional [ref 1](#)  
    non-organic [ref 1](#)  
    recurrent [ref 1](#)  
abetalipoproteinaemia [ref 1](#), [ref 2](#)  
ablepharon [ref 1](#)  
ABO system [ref 1](#)  
abortion [ref 1](#)  
Abortion Act 1967 [ref 1](#)  
absolute risk reduction [ref 1](#)  
absorption [ref 1](#), [ref 2](#)  
acanthosis nigricans [ref 1](#)  
accessory digit [ref 1](#)  
accident prevention [ref 1](#)  
acetylation status [ref 1](#)  
achalasia [ref 1](#)  
achondroplasia [ref 1](#), [ref 2](#)  
aciclovir [ref 1](#)  
acid-base status [ref 1](#)  
acne [ref 1](#)  
    neonatal [ref 1](#)  
acquired immune deficiency syndrome [ref 1](#)  
acrocentric chromosomes [ref 1](#)  
acrodermatitis enteropathica [ref 1](#)  
acute chest syndrome [ref 1](#)  
acute kidney injury [ref 1](#)  
acylcarnitines [ref 1](#)  
adaptive immunity [ref 1](#)  
Addison disease [ref 1](#), [ref 2](#)  
adenosine cyclic monophosphate (cAMP) [ref 1](#)  
adenotonsillar hypertrophy [ref 1](#)  
adenovirus [ref 1](#)

Adie syndrome [ref 1](#)  
adoption [ref 1](#)  
adrenal gland [ref 1](#)  
    anatomy [ref 1](#)  
    androgens [ref 1](#)  
    cortex [ref 1](#)  
    disorders of  
        Addison disease [ref 1](#)  
        phaeochromocytoma [ref 1](#)  
        glucocorticoids [ref 1](#)  
        mineralocorticoids [ref 1](#)  
adrenal hyperplasia [ref 1](#)  
adrenal insufficiency [ref 1](#), [ref 2](#)  
adrenal steroid excess [ref 1](#)  
adrenaline [ref 1](#)  
adrenarche [ref 1](#)  
adrenocorticotrophic hormone (ACTH) [ref 1](#)  
adverse drug reactions [ref 1](#)  
agenesis of corpus callosum [ref 1](#)  
airway [ref 1](#)  
    choking [ref 1](#)  
    inadequate protection [ref 1](#)  
    nasal [ref 1](#)  
    obstruction [ref 1](#), [ref 2](#)  
    opening procedures [ref 1](#)  
    oral [ref 1](#)  
Alagille syndrome [ref 1](#), [ref 2](#), [ref 3](#)  
albinism [ref 1](#)  
albumin [ref 1](#)  
alcohol [ref 1](#)  
Alexander syndrome [ref 1](#)  
alkaline phosphatase [ref 1](#)  
alkalosis [ref 1](#)  
allergic conjunctivitis [ref 1](#)  
allergic rhinitis [ref 1](#)  
alloimmune neonatal thrombocytopenia [ref 1](#)  
alopecia [ref 1](#)  
    scarring [ref 1](#)  
alopecia areata [ref 1](#), [ref 2](#)  
Alpers disease [ref 1](#)  
 $\alpha_1$ -antitrypsin deficiency [ref 1](#), [ref 2](#)  
Alport syndrome [ref 1](#)  
aluminium, abnormalities [ref 1](#)  
alveolar proteinosis [ref 1](#)  
ambiguous genitalia [ref 1](#), [ref 2](#)

*see also* intersex disorders

amblyopia [ref 1](#)

amenorrhoea [ref 1](#)

amino acid disorders [ref 1](#)

amino acid metabolism disorders [ref 1](#)

homocystinuria [ref 1](#)

maple syrup urine diseases [ref 1](#)

non-ketotic hyperglycinaemia [ref 1](#)

phenylketonuria [ref 1](#)

tyrosinaemia [ref 1](#)

amino acids [ref 1](#)

aminotransferases [ref 1](#)

ammonia [ref 1](#)

amniotic bands [ref 1](#)

amniotic fluid [ref 1](#)

amoebiasis [ref 1](#)

ampicillin [ref 1](#)

amputation [ref 1](#)

anaemia [ref 1](#), [ref 2](#), [ref 3](#)

aplastic [ref 1](#)

haemoglobin defects [ref 1](#)

hereditary haemolytic [ref 1](#)

iron deficiency [ref 1](#)

analysis of variance (ANOVA) [ref 1](#)

anaphylaxis [ref 1](#)

food-induced [ref 1](#)

anencephaly [ref 1](#)

aneuploid [ref 1](#)

Angelman syndrome [ref 1](#), [ref 2](#)

angio-oedema, hereditary [ref 1](#)

anion gap [ref 1](#)

aniridia [ref 1](#)

anisocoria [ref 1](#)

anisometropia [ref 1](#)

ankyloblepharon [ref 1](#)

anorectal atresia [ref 1](#)

anorectal malformations [ref 1](#)

anorexia nervosa [ref 1](#)

antenatal torsion [ref 1](#)

anterior horn cell disease [ref 1](#)

anterior wall defects [ref 1](#)

anthrax [ref 1](#)

anti-NMDA receptor encephalitis [ref 1](#)

anti-thymocyte globulin [ref 1](#)

antiarrhythmics [ref 1](#)

- antibiotics [ref 1](#)
- antibodies [ref 1](#)
  - deficiencies [ref 1](#)
- anticoagulants [ref 1](#)
  - natural [ref 1](#)
- anticonvulsants [ref 1](#)
- antigen presentation [ref 1](#)
- antigen recognition [ref 1](#)
- antigen-presenting cells [ref 1](#)
- antihistamines [ref 1](#)
- antral gastritis [ref 1](#)
- aortic arch, interruption of [ref 1](#)
- aortic coarctation *see* coarctation of aorta
- aortic stenosis [ref 1](#), [ref 2](#)
  - critical [ref 1](#)
- aortopulmonary window [ref 1](#)
- Apert syndrome [ref 1](#)
- aphakia [ref 1](#)
- aplastic anaemia [ref 1](#)
- aplastic crisis [ref 1](#)
- apnoea [ref 1](#)
- appendicitis [ref 1](#)
- appraisal [ref 1](#)
- aqueduct stenosis [ref 1](#)
- arginine vasopressin [ref 1](#)
- arrhythmias *see* cardiac arrhythmias
- arterial duct ligation [ref 1](#)
- arterial occlusion [ref 1](#)
- arterial pulse volume [ref 1](#)
- arthritis
  - enthesitis related [ref 1](#)
  - infectious [ref 1](#)
  - inflammatory bowel disease-related [ref 1](#)
  - juvenile idiopathic [ref 1](#)
  - juvenile psoriatic [ref 1](#)
  - oligoarticular [ref 1](#)
  - polyarticular [ref 1](#)
  - reactive [ref 1](#)
  - septic [ref 1](#), [ref 2](#)
  - systemic onset [ref 1](#)
- arthrogryposis multiplex congenita [ref 1](#)
- ascites [ref 1](#)
- Asperger syndrome [ref 1](#), [ref 2](#)
- aspergillosis [ref 1](#)
- asphyxiating thoracic dystrophy [ref 1](#)

aspirin [ref 1](#)  
    overdose [ref 1](#)  
asplenia [ref 1](#)  
asplenia syndrome [ref 1](#)  
asthma [ref 1](#), [ref 2](#)  
    acute attack [ref 1](#)  
    drug treatment [ref 1](#)  
    pathophysiology [ref 1](#)  
astigmatism [ref 1](#)  
astrocytoma [ref 1](#), [ref 2](#), [ref 3](#)  
asystole [ref 1](#)  
ataxia telangiectasia [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#)  
atazanavir [ref 1](#)  
atrial arrangement [ref 1](#)  
atrial isomerism [ref 1](#)  
atrial septal defect [ref 1](#), [ref 2](#)  
atrial situs [ref 1](#)  
atrioventricular connection [ref 1](#)  
atrioventricular septal defect [ref 1](#)  
    complete [ref 1](#)  
attention-deficit hyperactivity disorder [ref 1](#), [ref 2](#)  
audiogram [ref 1](#)  
audiometry  
    sweep [ref 1](#)  
    visual reinforced [ref 1](#)  
audit [ref 1](#)  
auditory brainstem response [ref 1](#)  
auscultation [ref 1](#)  
autism [ref 1](#)  
autistic spectrum disorder [ref 1](#)  
    assessment [ref 1](#)  
autofluorescence [ref 1](#)  
autoimmune haemolytic anaemia [ref 1](#)  
autoimmune hepatitis [ref 1](#)  
autoimmune polyglandular syndromes [ref 1](#)  
autonomy  
    of children [ref 1](#)  
    respect for [ref 1](#)  
autosomal dominant conditions [ref 1](#)  
autosomal recessive conditions [ref 1](#)  
autosomal recessive congenital agammaglobulinaemia [ref 1](#)  
auxology [ref 1](#)  
avian influenza virus [ref 1](#), [ref 2](#)  
azathioprine [ref 1](#)

B-cells [ref 1](#), [ref 2](#)  
developmental abnormalities [ref 1](#)  
Bacillus Calmette-Guérin (BCG) vaccine [ref 1](#), [ref 2](#)  
complications [ref 1](#)  
back pain [ref 1](#)  
Back to Sleep Campaign [ref 1](#)  
bacteraemia/septicaemia [ref 1](#)  
bacterial endocarditis [ref 1](#)  
bacterial overgrowth [ref 1](#)  
balanced translocations [ref 1](#)  
balloon atrial septostomy [ref 1](#)  
Bartter syndrome [ref 1](#)  
basophilic stippling [ref 1](#)  
basophils [ref 1](#)  
Batten disease [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#)  
Beau lines [ref 1](#)  
Becker muscular dystrophy [ref 1](#), [ref 2](#)  
Beckwith-Wiedemann syndrome [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#)  
behavioural problems in preschool children [ref 1](#)  
Behçet syndrome [ref 1](#), [ref 2](#)  
Bell's palsy [ref 1](#)  
beneficence [ref 1](#)  
benzyl alcohol [ref 1](#)  
best interests [ref 1](#)  
bias [ref 1](#)  
biliary atresia [ref 1](#), [ref 2](#)  
bilirubin [ref 1](#)  
metabolism [ref 1](#)  
bioavailability [ref 1](#)  
biopsy, skin [ref 1](#)  
birthmarks [ref 1](#)  
bladder  
extrophy [ref 1](#)  
neuropathic [ref 1](#)  
blepharophimosis [ref 1](#)  
blistering disorders [ref 1](#)  
autoimmune [ref 1](#)  
causes [ref 1](#)  
drug eruptions [ref 1](#)  
epidermolysis bullosa [ref 1](#)  
blood film [ref 1](#)  
blood gas measurement [ref 1](#)  
blood group antibodies [ref 1](#)  
blood product transfusion [ref 1](#)  
acute transfusion reactions [ref 1](#)

- massive transfusion reactions [ref 1](#)
- blood-brain barrier [ref 1](#)
- Bloom's syndrome [ref 1](#)
- body composition [ref 1](#)
  - puberty [ref 1](#)
- Bohr effect [ref 1](#)
- bone age [ref 1](#)
- bone and joint infections [ref 1](#)
- bone marrow transplantation [ref 1](#), [ref 2](#)
- bone metabolism [ref 1](#)
  - calcium and phosphate homeostasis [ref 1](#)
  - disorders of [ref 1](#)
  - investigation of abnormalities [ref 1](#)
- bone tumours [ref 1](#)
- bosentan [ref 1](#)
- botulism [ref 1](#), [ref 2](#)
- bovine spongiform encephalopathy [ref 1](#)
- brachial plexus injuries [ref 1](#)
- brachial plexus palsy [ref 1](#)
- bradycardia [ref 1](#), [ref 2](#)
- brain imaging [ref 1](#)
- brain tumours [ref 1](#)
- brainstem glioma [ref 1](#)
- brainstem tumours [ref 1](#)
- branchial arch remnants [ref 1](#)
- branching enzyme [ref 1](#)
- breast milk
  - composition of [ref 1](#)
  - drugs in [ref 1](#)
- breast-feeding [ref 1](#), [ref 2](#)
  - and allergy [ref 1](#)
  - contraindications [ref 1](#)
  - and diabetes [ref 1](#)
  - and infantile colic [ref 1](#)
  - and infection [ref 1](#)
  - and neurological development [ref 1](#)
- breast-milk jaundice [ref 1](#)
- breath-holding [ref 1](#), [ref 2](#)
- bronchiectasis [ref 1](#)
- bronchiolitis [ref 1](#), [ref 2](#)
  - obliterative [ref 1](#)
- bronchogenic cyst [ref 1](#), [ref 2](#)
- bronchopulmonary dysplasia [ref 1](#)
- brucellosis [ref 1](#)
- bruising [ref 1](#), [ref 2](#)

Brushfield spots [ref 1](#)  
bulimia nervosa [ref 1](#), [ref 2](#)  
bullous ichthyosiform erythroderma [ref 1](#)  
bullous pemphigoid [ref 1](#)  
bullying [ref 1](#)  
burns [ref 1](#), [ref 2](#)  
    assessment [ref 1](#)  
    chemical [ref 1](#)  
    epidemiology [ref 1](#)  
    inhalational injury [ref 1](#)  
    pathophysiology [ref 1](#)  
    transfer to burns centre [ref 1](#)  
    treatment [ref 1](#)  
button batteries [ref 1](#)

café-au-lait macules [ref 1](#)  
caffeine [ref 1](#)  
calcitonin [ref 1](#)  
calcitriol deficiency [ref 1](#)  
calcium [ref 1](#)  
Campath [ref 1](#)  
camptomelic dysplasia [ref 1](#)  
Canavan disease [ref 1](#), [ref 2](#), [ref 3](#)  
cancer *see* malignancy  
*Candida albicans* [ref 1](#)  
candidiasis [ref 1](#)  
    chronic mucocutaneous [ref 1](#), [ref 2](#)  
capillary haemangioma [ref 1](#), [ref 2](#)  
captopril [ref 1](#)  
carbamazepine [ref 1](#)  
carbohydrate metabolism [ref 1](#)  
    disorders of [ref 1](#)  
carbohydrates  
    digestion [ref 1](#)  
    intolerance [ref 1](#)  
carbon monoxide poisoning [ref 1](#)  
cardiac arrest  
    in-hospital [ref 1](#)  
    out-of-hospital [ref 1](#)  
cardiac arrhythmias [ref 1](#)  
    fetal [ref 1](#)  
cardiac catheterization [ref 1](#)  
    diagnostic [ref 1](#)  
    interventional [ref 1](#)  
cardiac obstruction



- in sick newborns [ref 1](#)
- in well children [ref 1](#)
- cardiac outlines [ref 1](#)
- cardiac output [ref 1](#)
- cardiac physiology [ref 1](#)
- cardiac rhythm, assessment of [ref 1](#)
- cardiology, fetal [ref 1](#)
- cardiovascular emergencies [ref 1](#)
  - bradyarrhythmia [ref 1](#)
  - inotropes [ref 1](#)
  - low cardiac output state [ref 1](#)
  - severe heart failure [ref 1](#)
  - shock [ref 1](#)
  - supraventricular tachycardia [ref 1](#)
  - tachycardia [ref 1](#)
  - ventricular tachycardia [ref 1](#)
- cardiovascular problems of neonate [ref 1](#)
- cardioversion [ref 1](#)
- Care Order [ref 1](#)
- Care Quality Commission (CQC) [ref 1](#)
- Caroli disease [ref 1](#)
- carotid thrill [ref 1](#)
- case-control studies [ref 1](#), [ref 2](#)
- cat-eye syndrome [ref 1](#)
- cat-scratch disease [ref 1](#)
- cataract [ref 1](#)
- CATCH 22 [ref 1](#)
- caustic ingestion [ref 1](#)
- CD4 T-cells [ref 1](#)
- CD8 T-cells [ref 1](#)
- CD40 ligand deficiency [ref 1](#)
- cellulitis
  - orbital [ref 1](#)
  - preseptal [ref 1](#)
- central nervous system
  - infections [ref 1](#)
  - tumours [ref 1](#)
- central tolerance [ref 1](#)
- central venous access [ref 1](#)
- central venous catheters, complications of [ref 1](#)
- cerebral palsy [ref 1](#), [ref 2](#)
  - feeding problems [ref 1](#)
- cerebrovascular disease [ref 1](#)
- cervical lymphadenopathy [ref 1](#), [ref 2](#), [ref 3](#)
- chalazion [ref 1](#)

- Chanarin-Dorfman syndrome [ref 1](#)
- Charcot-Marie-Tooth disease [ref 1](#)
- CHARGE syndrome [ref 1](#), [ref 2](#), [ref 3](#)
- Chédiak-Higashi syndrome [ref 1](#), [ref 2](#)
- chemical burns [ref 1](#)
- chemical conjunctivitis [ref 1](#)
- chemokines [ref 1](#)
- chemotherapy, effects of [ref 1](#)
- cherry-red spot [ref 1](#)
- chest compressions [ref 1](#)
- chest wall abnormalities [ref 1](#)
- chest wall deformities [ref 1](#)
- chest X-rays [ref 1](#)
- chi-squared test [ref 1](#)
- child abuse
  - physical abuse [ref 1](#)
  - types of [ref 1](#)
- Child Assessment Order [ref 1](#)
- child health surveillance [ref 1](#)
  - pre-school children [ref 1](#)
- child law [ref 1](#)
  - Children Act 1989 [ref 1](#), [ref 2](#)
  - children's capacity [ref 1](#)
  - consent [ref 1](#)
  - full legal capacity [ref 1](#)
  - guardians [ref 1](#)
  - 'ownership' of child [ref 1](#)
  - status of children in courts [ref 1](#)
  - wardship [ref 1](#)
- child protection [ref 1](#)
  - and confidentiality [ref 1](#)
- child protection and safeguarding [ref 1](#)
  - definition [ref 1](#)
  - emotional abuse [ref 1](#), [ref 2](#)
  - fabricated/induced illness [ref 1](#)
  - neglect [ref 1](#)
  - sexual abuse [ref 1](#), [ref 2](#)
- CHILD syndrome [ref 1](#)
- childhood vasculitis [ref 1](#)
- children
  - autonomy [ref 1](#)
  - and confidentiality [ref 1](#)
  - moral status of [ref 1](#)
  - 'ownership' of [ref 1](#)
  - research in [ref 1](#)

rights of [ref 1](#)

status on courts [ref 1](#)

*see also* child law

Children Act 1989 [ref 1](#), [ref 2](#), [ref 3](#)

children's capacity [ref 1](#)

16–17 years [ref 1](#)

Fraser guidelines [ref 1](#)

intervening years [ref 1](#)

preschool [ref 1](#)

*Chlamydia trachomatis* [ref 1](#)

chloramphenicol, grey-baby syndrome [ref 1](#)

chlorpromazine [ref 1](#)

choanal atresia [ref 1](#), [ref 2](#), [ref 3](#)

choking [ref 1](#)

cholecystokinin-pancreozymin [ref 1](#)

Christmas disease [ref 1](#)

chromium, abnormalities [ref 1](#)

chromosomes [ref 1](#)

autosomal chromosome aneuploidies [ref 1](#)

comparative genomic hybridization [ref 1](#)

FISH testing [ref 1](#)

genetic counselling [ref 1](#)

microdeletion syndromes [ref 1](#)

multiplex ligation-dependent probe amplification [ref 1](#)

quantitative fluorescence polymerase chain reaction [ref 1](#)

sex chromosome aneuploidies [ref 1](#)

chronic bullous dermatosis of childhood [ref 1](#)

chronic fatigue syndrome [ref 1](#)

aetiology [ref 1](#)

clinical features [ref 1](#)

diagnostic criteria [ref 1](#)

epidemiology [ref 1](#)

initial assessment [ref 1](#)

investigation [ref 1](#)

management [ref 1](#)

prognosis [ref 1](#)

chronic granulomatous disease [ref 1](#)

Churg-Strauss syndrome [ref 1](#)

chylomicrons [ref 1](#)

chylothorax [ref 1](#)

circulation, checking [ref 1](#)

class-switch recombination [ref 1](#)

defects in [ref 1](#)

cleft lip and palate [ref 1](#)

clinical effectiveness [ref 1](#)

- clinical governance [ref 1](#)
  - education, appraisal and revalidation [ref 1](#)
  - history [ref 1](#)
  - outcome and experience [ref 1](#)
  - patient experience [ref 1](#)
  - patient safety [ref 1](#)
- Clinical Negligence Scheme for Trusts (CNST) [ref 1](#)
- clinical pharmacology [ref 1](#)
  - adverse drug reactions [ref 1](#)
  - drug interactions [ref 1](#)
  - drug monitoring [ref 1](#)
  - formulation [ref 1](#)
  - intravenous drugs [ref 1](#)
  - paediatric dosing [ref 1](#)
  - pharmacokinetics and pharmacodynamics [ref 1](#)
  - prescribing outside licence [ref 1](#)
- clobazam [ref 1](#)
- clonazepam [ref 1](#)
- clozapine [ref 1](#)
- clubbing [ref 1](#)
- coagulase-negative staphylococci [ref 1](#)
- coagulation [ref 1](#)
- coagulation disorders [ref 1](#)
  - neonate [ref 1](#)
- coagulopathy [ref 1](#)
- coarctation of aorta [ref 1](#), [ref 2](#)
  - adult-type [ref 1](#)
  - repair [ref 1](#)
- Coat disease [ref 1](#)
- Cockayne's syndrome [ref 1](#), [ref 2](#)
- coeliac disease [ref 1](#)
- cognitive behavioural therapy [ref 1](#)
- cohort studies [ref 1](#), [ref 2](#)
- cold-induced injuries [ref 1](#)
- collecting duct [ref 1](#), [ref 2](#)
- collodion baby [ref 1](#)
- coloboma [ref 1](#), [ref 2](#), [ref 3](#)
- colon [ref 1](#)
- colonic atresia [ref 1](#)
- colour vision [ref 1](#)
- coma
  - non-traumatic [ref 1](#)
  - thiopentone-induced [ref 1](#)
- combined immunodeficiency [ref 1](#)
- common lymphoid progenitor [ref 1](#)

common myeloid progenitor [ref 1](#)  
common variable immunodeficiency [ref 1](#)  
communication [ref 1](#), [ref 2](#)  
comparative genomic hybridization [ref 1](#)  
complement [ref 1](#), [ref 2](#)  
    deficiency [ref 1](#)  
computerized axial tomography [ref 1](#)  
conduct disorders [ref 1](#)  
confidence intervals [ref 1](#)  
confidentiality [ref 1](#)  
    and child protection [ref 1](#)  
    and children [ref 1](#)  
    contraception in teenagers [ref 1](#)  
confounding [ref 1](#)  
congenital adrenal hyperplasia [ref 1](#)  
congenital cystic adenomatoid malformation [ref 1](#), [ref 2](#)  
congenital facial paralysis [ref 1](#)  
congenital heart disease [ref 1](#)  
    bypass surgery [ref 1](#)  
    drug therapy [ref 1](#)  
    epidemiology [ref 1](#)  
    examination [ref 1](#)  
    non-bypass surgery [ref 1](#)  
    physiology [ref 1](#)  
    syndromes [ref 1](#)  
congenital infections [ref 1](#)  
congenital lobar emphysema [ref 1](#), [ref 2](#)  
congenital myopathies [ref 1](#)  
congenital pulmonary lymphangiectasia [ref 1](#)  
conjunctivitis [ref 1](#)  
    neonatal [ref 1](#)  
Conn syndrome [ref 1](#)  
connective tissue disorders [ref 1](#)  
consanguinity [ref 1](#)  
consent [ref 1](#)  
    contraception in teenagers [ref 1](#)  
    ethical basis [ref 1](#)  
consequentialism [ref 1](#)  
constipation [ref 1](#)  
contact dermatitis [ref 1](#)  
contraception in teenagers [ref 1](#)  
convulsions [ref 1](#)  
    pathophysiology [ref 1](#)  
    treatment [ref 1](#)  
Coombs test [ref 1](#)

copper, abnormalities [ref 1](#), [ref 2](#)  
cornea [ref 1](#)  
    clouding [ref 1](#)  
    deposits [ref 1](#)  
    developmental abnormalities [ref 1](#)  
    keratitis [ref 1](#)  
    keratoconus [ref 1](#)  
Cornelia de Lange syndrome [ref 1](#)  
correlation coefficients [ref 1](#)  
cortisol [ref 1](#)  
cover test [ref 1](#)  
cows' milk protein intolerance [ref 1](#)  
cows' milk protein sensitive enteropathy [ref 1](#)  
cranial nerve lesions [ref 1](#)  
craniopharyngioma [ref 1](#), [ref 2](#), [ref 3](#)  
craniosynostosis [ref 1](#)  
creatinine clearance [ref 1](#)  
Creutzfeldt-Jakob disease, new variant [ref 1](#)  
cri du chat syndrome [ref 1](#)  
Crigler-Najjar syndrome [ref 1](#)  
Crohn's disease [ref 1](#)  
cross-sectional studies [ref 1](#)  
crossing over [ref 1](#)  
crossover studies [ref 1](#)  
croup [ref 1](#)  
Crouzon syndrome [ref 1](#)  
crush injuries [ref 1](#)  
cryptophthalmus [ref 1](#)  
Cushing syndrome [ref 1](#)  
cyanosis [ref 1](#), [ref 2](#)  
    of newborn [ref 1](#)  
cyclosporin [ref 1](#)  
cystic adenomatoid malformation [ref 1](#)  
cystic fibrosis [ref 1](#), [ref 2](#), [ref 3](#)  
    diagnosis [ref 1](#)  
    genetics [ref 1](#)  
    presentation and management [ref 1](#)  
    transplantation [ref 1](#)  
cystic hygroma [ref 1](#)  
cystinosis [ref 1](#), [ref 2](#)  
cystinuria [ref 1](#)  
cytokines [ref 1](#), [ref 2](#)  
cytomegalovirus [ref 1](#), [ref 2](#), [ref 3](#), 876  
    congenital [ref 1](#), [ref 2](#)  
    and fetal malformations [ref 1](#)

cytotoxic T-cells [ref 1](#)

dacluzimab [ref 1](#)

dacryocystitis [ref 1](#)

Dandy-Walker malformation [ref 1](#)

De Morsier syndrome [ref 1](#)

deafness [ref 1](#)

debrancher enzyme [ref 1](#)

dehydration [ref 1](#)

dendritic cells [ref 1](#)

Dengue fever [ref 1](#)

deontology [ref 1](#)

depression [ref 1](#)

dermatitis artefacta [ref 1](#)

dermatitis herpetiformis [ref 1](#)

dermatology [ref 1](#)

- birthmarks [ref 1](#)
- blistering disorders [ref 1](#)
- erythemas [ref 1](#)
- hair, nails and teeth [ref 1](#)
- ichthyoses [ref 1](#)
- neonatal skin disorders [ref 1](#)
- photosensitive disorders [ref 1](#)
- pigmentation disorders [ref 1](#)
- rashes [ref 1](#)
- structure and function of skin [ref 1](#)

dermatomyositis [ref 1](#)

dermis [ref 1](#)

developmental abnormalities [ref 1](#)

developmental assessment [ref 1](#)

developmental coordination disorder [ref 1](#)

developmental delay [ref 1](#), [ref 2](#)

- causes [ref 1](#)

developmental disabilities [ref 1](#)

- attention-deficit hyperactivity disorder [ref 1](#)
- autism [ref 1](#)
- deficits in attention, motor control and perception [ref 1](#)
- learning disability [ref 1](#)

developmental dysplasia of hip [ref 1](#)

developmental examination [ref 1](#)

developmental milestones [ref 1](#)

dextrocardia [ref 1](#)

Di George syndrome [ref 1](#), [ref 2](#), [ref 3](#)

diabetes insipidus [ref 1](#)

- nephrogenic [ref 1](#)

- treatment [ref 1](#)
- diabetes mellitus [ref 1](#)
  - aetiology [ref 1](#)
  - beta-cell failure [ref 1](#)
  - and breast-feeding [ref 1](#)
  - causes [ref 1](#)
  - diagnosis [ref 1](#)
  - epidemiology [ref 1](#)
  - and fetal malformations [ref 1](#)
  - long-term complications [ref 1](#)
  - management [ref 1](#)
  - maternal, effects on fetus and newborn [ref 1](#)
  - presentation [ref 1](#)
  - risk factors for type 2 [ref 1](#)
- diabetic ketoacidosis [ref 1](#)
- diabetic retinopathy [ref 1](#)
- dialysis [ref 1](#)
- diaphragm, eventration [ref 1](#)
- diaphragmatic hernia [ref 1](#)
  - congenital [ref 1](#), [ref 2](#)
- diarrhoea
  - chronic [ref 1](#)
  - travellers' [ref 1](#)
- diazepam
  - absorption and  $pK_a$  [ref 1](#)
  - half-life [ref 1](#)
- didanosine [ref 1](#)
- diet, in diabetes mellitus [ref 1](#)
- dilated cardiomyopathy [ref 1](#)
- diphtheria vaccine [ref 1](#), [ref 2](#)
- diploid [ref 1](#)
- dipyridamole [ref 1](#), [ref 2](#)
- direct antiglobulin test [ref 1](#)
- disaccharide absorption disorders [ref 1](#)
- disseminated intravascular coagulation [ref 1](#)
- distal arthrogryposis syndrome [ref 1](#)
- distal tubule [ref 1](#), [ref 2](#)
- distribution [ref 1](#)
- diuretics [ref 1](#)
- DNA [ref 1](#)
- dobutamine [ref 1](#)
- doctors
  - moral conflicts [ref 1](#)
  - moral duties [ref 1](#)
- dopamine [ref 1](#)



Down syndrome [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#), [ref 5](#), [ref 6](#)  
drowning [ref 1](#)  
    pathophysiology [ref 1](#)  
    prognostic signs [ref 1](#)  
    re-warming [ref 1](#)  
    treatment [ref 1](#)  
drug eruptions [ref 1](#)  
drug interactions [ref 1](#)  
drug monitoring [ref 1](#)  
drug-induced liver disease [ref 1](#)  
dry eye [ref 1](#)  
DTPA scan [ref 1](#)  
Duchenne muscular dystrophy [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#)  
Duncan syndrome [ref 1](#)  
duodenal atresia [ref 1](#)  
duodenal obstruction [ref 1](#)  
duplex kidney [ref 1](#)  
dying spells [ref 1](#)  
dyskeratosis congenita [ref 1](#)  
dysmotility [ref 1](#)  
dysphagia [ref 1](#)  
dyspraxia [ref 1](#)  
dystonia [ref 1](#)  
dystrophic myotonia [ref 1](#)  
  
ears [ref 1](#)  
    perforated eardrum [ref 1](#)  
eating disorders [ref 1](#)  
Ebstein anomaly [ref 1](#), [ref 2](#)  
ECG [ref 1](#)  
echinocandins [ref 1](#)  
echocardiography [ref 1](#)  
ectodermal dysplasias [ref 1](#), [ref 2](#)  
ectopia lentis [ref 1](#)  
ectropion [ref 1](#)  
eczema, atopic [ref 1](#)  
    associated conditions [ref 1](#)  
    differential diagnosis [ref 1](#)  
    features [ref 1](#)  
    management [ref 1](#)  
Edward syndrome [ref 1](#), [ref 2](#)  
efavirenz [ref 1](#)  
effector T cells [ref 1](#)  
Eisenmenger syndrome [ref 1](#)  
electro-oculography [ref 1](#)

- electrocution injury [ref 1](#)
- electroencephalography [ref 1](#)
- electrolyte disturbances [ref 1](#)
- electroretinography [ref 1](#)
- Ellis van Crefeld syndrome [ref 1](#)
- Embden-Meyerhof pathway [ref 1](#)
- embryology
  - cardiovascular system [ref 1](#)
  - central nervous system [ref 1](#)
  - gastrointestinal system [ref 1](#)
  - genitourinary system [ref 1](#)
  - renal system [ref 1](#)
  - respiratory system [ref 1](#)
- emergencies
  - airway [ref 1](#)
  - burns [ref 1](#)
  - cardiovascular [ref 1](#)
  - cold-induced injuries [ref 1](#)
  - convulsions [ref 1](#)
  - drowning [ref 1](#)
  - electrocution injury [ref 1](#)
  - non-traumatic coma [ref 1](#)
  - respiratory failure [ref 1](#)
- resuscitation
  - cardiac arrest [ref 1](#)
  - post-resuscitation management [ref 1](#)
  - when to stop [ref 1](#)
- severe head injury [ref 1](#)
- trauma [ref 1](#)

Emergency Protection Order [ref 1](#)

Emery-Dreifuss muscular dystrophy [ref 1](#)

emollients [ref 1](#)

emotional abuse [ref 1](#), [ref 2](#)

empyema [ref 1](#)

encephalitis [ref 1](#), [ref 2](#)

- mycoplasma [ref 1](#)

encephalocele [ref 1](#)

encephalopathy, neonatal [ref 1](#)

encopresis and soiling [ref 1](#)

endocarditis

- bacterial [ref 1](#)
- infective [ref 1](#)

endocrine problems of neonate [ref 1](#)

energy balance [ref 1](#)

enteral nutrition [ref 1](#), [ref 2](#)

choice of feed regimen [ref 1](#)

choice of feed type [ref 1](#)

dysmotility [ref 1](#)

indications for [ref 1](#)

methods of feed delivery [ref 1](#)

enteric fever [ref 1](#)

enterohepatic circulation [ref 1](#)

enteroviruses [ref 1](#)

entropion [ref 1](#)

enuresis [ref 1](#)

enzymology [ref 1](#)

eosinophilia [ref 1](#)

eosinophilic enterocolitis [ref 1](#)

eosinophilic oesophagitis [ref 1](#)

eosinophilic pustular folliculitis [ref 1](#)

eosinophils [ref 1](#)

ependymoma [ref 1](#)

epicanthus [ref 1](#)

epidermis [ref 1](#)

epidermolysis bullosa [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#)

epidermolysis bullosa acquisita [ref 1](#)

epigastric hernia [ref 1](#)

epiglottitis [ref 1](#)

epilepsy [ref 1](#)

assessment and treatment [ref 1](#)

definition and classification [ref 1](#)

diagnosis [ref 1](#)

generalized [ref 1](#)

partial [ref 1](#)

prognosis [ref 1](#)

*see also* seizures

episcleritis [ref 1](#)

epispadias [ref 1](#)

epistaxis [ref 1](#)

Epstein-Barr virus [ref 1](#)

Erb's palsy [ref 1](#)

erythema infectiosum [ref 1](#)

erythema marginatum [ref 1](#)

erythema migrans [ref 1](#)

erythema multiforme [ref 1](#), [ref 2](#)

erythema nodosum [ref 1](#), [ref 2](#)

erythema toxicum neonatorum [ref 1](#)

erythropoietin system [ref 1](#)

*Escherichia coli* [ref 1](#)

esotropia [ref 1](#)

- etanercept [ref 1](#)
- ethics
  - ethical issues, technology and law [ref 1](#)
  - and law [ref 1](#)
  - moral theories [ref 1](#)
  - principles [ref 1](#)
- ethosuximide [ref 1](#)
- eventration of diaphragm [ref 1](#)
- evoked potentials [ref 1](#)
- Ewing sarcoma [ref 1](#)
- exanthem subitum [ref 1](#)
- exchange transfusion [ref 1](#)
- exocrine pancreatic insufficiency [ref 1](#)
- exome sequencing [ref 1](#)
- exomphalos [ref 1](#), [ref 2](#)
- exotropia [ref 1](#)
- experimental studies [ref 1](#)
- extracellular fluid volume [ref 1](#)
- extracorporeal membrane oxygenation [ref 1](#), [ref 2](#)
- extremely premature infants [ref 1](#)
- eye [ref 1](#)
  - anterior chamber [ref 1](#)
  - conjunctiva [ref 1](#)
  - cornea [ref 1](#)
  - extraocular muscles [ref 1](#)
  - globe [ref 1](#)
  - lens [ref 1](#)
  - orbits [ref 1](#)
  - retina [ref 1](#)
  - sclera [ref 1](#)
  - uvea tract [ref 1](#)
  - vitreous [ref 1](#)
- eye examination [ref 1](#), [ref 2](#)
  - colour vision [ref 1](#)
  - electrophysiology [ref 1](#)
  - refractive errors [ref 1](#)
  - visual assessment [ref 1](#)
  - visual fields [ref 1](#)
- eye movement disorders [ref 1](#), [ref 2](#)
  - nystagmus [ref 1](#), [ref 2](#)
  - squint [ref 1](#)
- eyelid abnormalities [ref 1](#)
  - congenital [ref 1](#)
  - haemangiomas [ref 1](#)
  - infections and inflammation [ref 1](#)

Marcus Gunn jaw-winking syndrome [ref 1](#)

myasthenia gravis [ref 1](#)

ptosis [ref 1](#)

fabricated/induced illness [ref 1](#)

Fabry disease [ref 1](#), [ref 2](#)

facial nerve paralysis [ref 1](#)

facio-scapulohumeral muscular dystrophy [ref 1](#), [ref 2](#)

faecal  $\alpha_1$ -antitrypsin [ref 1](#)

faltering growth [ref 1](#)

human immunodeficiency virus [ref 1](#)

familial adenomatous polyposis coli [ref 1](#)

familial combined hyperlipidaemia [ref 1](#)

Fanconi syndrome [ref 1](#), [ref 2](#)

fat

body content [ref 1](#)

digestion [ref 1](#)

metabolism [ref 1](#)

subcutaneous [ref 1](#)

fat oxidation disorders [ref 1](#)

fat-soluble vitamins [ref 1](#)

feeding problems [ref 1](#)

femoral fractures [ref 1](#)

fetal alcohol syndrome [ref 1](#), [ref 2](#)

fetal haemoglobin [ref 1](#)

fetal retinoic acid [ref 1](#)

fetal teratogens [ref 1](#)

infectious agents [ref 1](#)

maternal illness [ref 1](#)

fetal valproate syndrome [ref 1](#)

fetal warfarin syndrome [ref 1](#)

fetus

adaptation to extrauterine life [ref 1](#)

circulatory changes at birth [ref 1](#)

echocardiography [ref 1](#)

growth [ref 1](#)

renal function [ref 1](#)

see also fetal

Fifth disease *see* parvovirus B19

first-order kinetics [ref 1](#)

first-pass metabolism [ref 1](#)

Fisher exact test [ref 1](#)

floppy infant [ref 1](#)

fluorescence in-situ hybridization (FISH) [ref 1](#)

folate, nutritional requirement [ref 1](#)

follicle-stimulating hormone [ref 1](#)

Fontan operation [ref 1](#)  
food intolerance [ref 1](#)  
foot drop [ref 1](#)  
foreign bodies  
    inhaled [ref 1](#)  
    oesophageal [ref 1](#)  
formula milk [ref 1](#)  
    composition of [ref 1](#)  
formulation [ref 1](#)  
fostering [ref 1](#)  
fractures [ref 1](#)  
    femoral [ref 1](#)  
    humerus [ref 1](#)  
    lower limb [ref 1](#)  
    metaphyseal [ref 1](#)  
    ribs [ref 1](#)  
    skull [ref 1](#)  
    upper limb [ref 1](#)  
fragile X syndrome [ref 1](#), [ref 2](#)  
Fraser guidelines [ref 1](#)  
free-field testing [ref 1](#)  
frenulum, torn [ref 1](#)  
Friedreich ataxia [ref 1](#), [ref 2](#)  
frostbite [ref 1](#)  
Fukuyama congenital muscular dystrophy [ref 1](#)  
fungal infections [ref 1](#)

G-protein receptors [ref 1](#)  
gabapentin [ref 1](#)  
galactosaemia [ref 1](#)  
 $\gamma$ -glutamyltransferase [ref 1](#)  
Gardener syndrome [ref 1](#)  
gasping syndrome [ref 1](#)  
gastric inhibitory peptide [ref 1](#)  
gastrin [ref 1](#)  
gastro-oesophageal reflux [ref 1](#), [ref 2](#), [ref 3](#)  
    differential diagnosis [ref 1](#)  
    investigation [ref 1](#)  
    management [ref 1](#)  
    symptoms and signs [ref 1](#)  
gastroenteritis [ref 1](#)  
gastrointestinal bleeding [ref 1](#)  
gastrointestinal problems of newborn [ref 1](#)  
gastrointestinal surgery [ref 1](#)  
gastrointestinal system, congenital abnormalities [ref 1](#)

gastroschisis [ref 1](#), [ref 2](#)  
gastrostomy [ref 1](#)  
    tube feeding [ref 1](#)  
Gaucher disease [ref 1](#), [ref 2](#), [ref 3](#)  
gene therapy [ref 1](#)  
genetic counselling [ref 1](#), [ref 2](#)  
genetic testing [ref 1](#)  
genetics  
    ambiguous genitalia [ref 1](#)  
    chromosomes [ref 1](#)  
    fetal teratogens [ref 1](#)  
    genomic imprinting [ref 1](#)  
    mendelian inheritance [ref 1](#)  
    mitochondrial disorders [ref 1](#)  
    molecular genetics [ref 1](#)  
    preimplantation genetic diagnosis [ref 1](#)  
    prenatal testing [ref 1](#)  
    trinucleotide repeat disorders [ref 1](#)  
genitourinary problems of newborn [ref 1](#)  
genomic imprinting [ref 1](#)  
germ-cell tumours [ref 1](#)  
German measles *see* rubella  
giardiasis [ref 1](#), [ref 2](#)  
Gilbert syndrome [ref 1](#)  
Gilles de la Tourette syndrome [ref 1](#)  
Gillick principle [ref 1](#)  
Gitelman syndrome [ref 1](#)  
Glasgow Coma Scale [ref 1](#), [ref 2](#)  
glaucoma [ref 1](#), [ref 2](#)  
glomerular filtration rate [ref 1](#)  
glomerulonephritis [ref 1](#)  
    acute post-streptococcal [ref 1](#)  
glucocorticoids [ref 1](#)  
gluconeogenesis [ref 1](#)  
glucose 6-phosphatase deficiency [ref 1](#)  
glucose 6-phosphate dehydrogenase deficiency [ref 1](#), [ref 2](#)  
glucose 6-phosphate translocase deficiency [ref 1](#)  
glucose homeostasis [ref 1](#)  
    diabetes mellitus [ref 1](#)  
    physiology [ref 1](#)  
glucose-galactose malabsorption [ref 1](#)  
glutaric aciduria type 1 [ref 1](#), [ref 2](#)  
glycogen metabolism [ref 1](#)  
glycogen storage disease [ref 1](#)  
glycolysis [ref 1](#), [ref 2](#)

glycosylation, congenital disorders [ref 1](#)  
Goldenhar syndrome [ref 1](#)  
'golf balls' [ref 1](#)  
gonadotrophins [ref 1](#)  
granulocytes [ref 1](#)  
granuloma annulare [ref 1](#)  
Graves' disease [ref 1](#)  
greenstick fractures [ref 1](#)  
grey matter disorders [ref 1](#)  
grey-baby syndrome [ref 1](#)  
group B streptococcus [ref 1](#)  
growth [ref 1](#)  
    assessment and investigation [ref 1](#)  
    faltering [ref 1](#)  
    postnatal [ref 1](#)  
    prenatal [ref 1](#)  
growth disorders [ref 1](#)  
    short stature [ref 1](#)  
    tall stature [ref 1](#)  
growth hormone [ref 1](#)  
    provocation tests [ref 1](#)  
    treatment [ref 1](#)  
guanine cyclic monophosphate (cGMP) [ref 1](#)  
guardians [ref 1](#)  
Guillain-Barré syndrome [ref 1](#), [ref 2](#)  
gunshot wounds [ref 1](#)  
gut hormones [ref 1](#)  
gynaecomastia [ref 1](#)

HAART therapy [ref 1](#)  
haemangioma [ref 1](#)  
    laryngeal [ref 1](#)  
haemangiomas, multiple small [ref 1](#)  
haematology/coagulation problems of neonate [ref 1](#)  
haematopoietic stem cells [ref 1](#)  
haematuria [ref 1](#), [ref 2](#)  
haemoglobin  
    abnormalities [ref 1](#)  
    defects [ref 1](#)  
    oxygen-dissociation curve [ref 1](#)  
    synthesis [ref 1](#)  
haemolysis [ref 1](#)  
haemolytic disease of newborn [ref 1](#)  
haemolytic-uraemic syndrome [ref 1](#)  
haemophagocytic lymphohistiocytosis [ref 1](#)



haemophilia [ref 1](#), [ref 2](#)  
*Haemophilus influenzae* type B vaccine [ref 1](#)  
haemorrhagic disease of newborn [ref 1](#), [ref 2](#)  
haemosiderosis [ref 1](#)  
hair [ref 1](#)  
half-life [ref 1](#)  
haloperidol [ref 1](#)  
hantaviruses [ref 1](#)  
haploid [ref 1](#), [ref 2](#)  
Happle syndrome [ref 1](#)  
harlequin ichthyosis [ref 1](#)  
Hartnup's disease [ref 1](#)  
Hb C disease [ref 1](#)  
Hb D disease [ref 1](#)  
Hb E disease [ref 1](#)  
head injury [ref 1](#), [ref 2](#), [ref 3](#)  
    cerebral perfusion pressure [ref 1](#)  
    complications in intensive care [ref 1](#)  
    imaging [ref 1](#)  
    mild closed [ref 1](#)  
    non-accidental [ref 1](#)  
    raised intracranial pressure [ref 1](#)  
    severe closed [ref 1](#)  
head lice [ref 1](#)  
head and neck surgery [ref 1](#)  
head shape, abnormal [ref 1](#)  
headaches [ref 1](#)  
    migraine [ref 1](#)  
    non-organic [ref 1](#)  
    tension [ref 1](#)  
Heaf test [ref 1](#)  
hearing [ref 1](#)  
hearing tests [ref 1](#)  
heart  
    anatomy [ref 1](#)  
    globular [ref 1](#)  
    innocent murmurs [ref 1](#)  
    murmurs [ref 1](#)  
    muscle physiology [ref 1](#)  
    rate [ref 1](#), [ref 2](#)  
    rhythm [ref 1](#)  
    sounds [ref 1](#)  
    *see also* cardiac; cardio  
heart block [ref 1](#)  
heart disease, acquired [ref 1](#)

heart failure [ref 1](#), [ref 2](#)  
drug therapy [ref 1](#)  
heart-lung transplantation [ref 1](#)  
*Helicobacter pylori* [ref 1](#)  
hemihypertrophy [ref 1](#)  
Henoch-Schönlein nephritis [ref 1](#)  
Henoch-Schönlein purpura [ref 1](#), [ref 2](#)  
heparin [ref 1](#)  
hepatic metabolism [ref 1](#)  
hepatitis  
acute [ref 1](#)  
acute infective [ref 1](#)  
autoimmune [ref 1](#)  
chronic viral [ref 1](#)  
idiopathic neonatal [ref 1](#)  
hepatitis A [ref 1](#)  
hepatitis B [ref 1](#)  
congenital [ref 1](#)  
vaccine [ref 1](#), [ref 2](#)  
hepatitis C [ref 1](#)  
hepatoblastoma [ref 1](#)  
hepatology [ref 1](#)  
acute hepatitis [ref 1](#)  
acute liver failure [ref 1](#)  
chronic liver disease [ref 1](#)  
jaundice in infancy [ref 1](#)  
pancreas [ref 1](#)  
hepatomegaly [ref 1](#)  
hepatopulmonary syndrome [ref 1](#), [ref 2](#)  
hepatorenal syndrome [ref 1](#)  
hepatosplenomegaly [ref 1](#)  
hereditary elliptocytosis [ref 1](#)  
hereditary fructose intolerance [ref 1](#)  
hereditary haemolytic anaemia [ref 1](#)  
hereditary spherocytosis [ref 1](#)  
herpes simplex encephalitis [ref 1](#)  
herpes simplex virus [ref 1](#), [ref 2](#)  
congenital [ref 1](#)  
heterochromia iridis [ref 1](#)  
heterotropia [ref 1](#)  
Hirschsprung disease [ref 1](#), [ref 2](#), [ref 3](#)  
hirsutism [ref 1](#), [ref 2](#)  
HIV, ocular manifestations [ref 1](#)  
Hodgkin lymphoma [ref 1](#)  
holoprosencephaly [ref 1](#)

Holt-Oram syndrome [ref 1](#)  
homocystinuria [ref 1](#), [ref 2](#)  
homologues [ref 1](#)  
hookworm [ref 1](#)  
hordeolum [ref 1](#)  
hormonal problems [ref 1](#)  
hormone-binding proteins [ref 1](#)  
hormone-receptor interactions [ref 1](#)  
hormones [ref 1](#)  
    adrenal gland [ref 1](#), [ref 2](#)  
    anterior pituitary [ref 1](#)  
    control and feedback [ref 1](#)  
    gut [ref 1](#)  
    mode of transmission [ref 1](#)  
    puberty [ref 1](#)  
    regulation [ref 1](#)  
    secretion [ref 1](#)  
    thyroid gland [ref 1](#)  
    transport and metabolism [ref 1](#)  
Horner syndrome [ref 1](#), [ref 2](#)  
horseshoe kidney [ref 1](#)  
human chorionic gonadotrophin [ref 1](#)  
human immunodeficiency virus [ref 1](#)  
    babies of HIV-positive mother [ref 1](#)  
    clinical manifestations [ref 1](#)  
    diagnosis [ref 1](#)  
    faltering growth [ref 1](#)  
    follow-up of HIV-positive children [ref 1](#)  
    HIV encephalopathy [ref 1](#)  
    lymphocytic interstitial pneumonitis [ref 1](#)  
    neonatal [ref 1](#)  
    opportunistic infections [ref 1](#)  
    recurrent bacterial infections [ref 1](#)  
    thrombocytopenia [ref 1](#)  
    transmission [ref 1](#)  
    treatment [ref 1](#)  
human papillomavirus vaccine [ref 1](#)  
human placental lactogen [ref 1](#)  
Human Rights Act 1998 [ref 1](#)  
humerus, fractures [ref 1](#)  
Hunter syndrome [ref 1](#)  
Huntington chorea [ref 1](#)  
Hurler syndrome [ref 1](#), [ref 2](#)  
hydroceles [ref 1](#)  
hydrocephalus [ref 1](#)

hydrogen breath testing [ref 1](#)  
hydronephrosis [ref 1](#)  
hydrops fetalis [ref 1](#), [ref 2](#)  
hyper IgE syndrome [ref 1](#), [ref 2](#)  
hyperammonaemia [ref 1](#), [ref 2](#)  
hyperbilirubinaemia  
    conjugated [ref 1](#)  
    unconjugated [ref 1](#)  
hypercalcaemia [ref 1](#), [ref 2](#)  
hypercholesterolaemias [ref 1](#)  
hyperinsulinism [ref 1](#)  
hyperkalaemia [ref 1](#)  
hyperkeratotic eczema [ref 1](#)  
hypermetropia [ref 1](#)  
hypermobility [ref 1](#)  
hypernatraemia [ref 1](#)  
hyperphosphataemia [ref 1](#), [ref 2](#)  
hyperpigmentation [ref 1](#)  
hypersensitivity reactions [ref 1](#)  
hypersplenism [ref 1](#)  
hypertelorism [ref 1](#)  
hypertension [ref 1](#), [ref 2](#), [ref 3](#)  
    treatment [ref 1](#)  
hypertensive retinopathy [ref 1](#)  
hyperthyroidism [ref 1](#)  
    management [ref 1](#)  
hypertrichosis [ref 1](#), [ref 2](#)  
hypertriglyceridaemias [ref 1](#)  
hypertrophic cardiomyopathy [ref 1](#)  
hypertrophic obstructive cardiomyopathy [ref 1](#)  
hypocalcaemia [ref 1](#), [ref 2](#)  
hypocalciuria [ref 1](#)  
hypochondroplasia [ref 1](#)  
hypogammaglobulinaemia, transient of infancy [ref 1](#)  
hypoglycaemia [ref 1](#), [ref 2](#)  
    neonatal [ref 1](#)  
hypokalaemia [ref 1](#)  
hypomagnesaemia [ref 1](#), [ref 2](#)  
hypomelanosis of Ito [ref 1](#)  
hyponatraemia [ref 1](#)  
hypoparathyroidism [ref 1](#), [ref 2](#)  
hypophosphataemia [ref 1](#)  
hypopigmentation [ref 1](#)  
hypoplastic left heart syndrome [ref 1](#)  
hypospadias [ref 1](#), 858

hypotelorism [ref 1](#)  
hypotension [ref 1](#)  
hypothalamus, anatomy [ref 1](#)  
hypothermia [ref 1](#)  
hypothyroidism [ref 1](#), [ref 2](#)  
    congenital [ref 1](#)  
    management [ref 1](#)  
hypotonia [ref 1](#)  
hypoxia, chronic [ref 1](#)  
hypoxic-ischaemic encephalopathy [ref 1](#)

ichthyoses [ref 1](#)  
    collodion baby [ref 1](#)  
    harlequin [ref 1](#)  
    inherited [ref 1](#)  
ichthyosis vulgaris [ref 1](#)  
idiopathic juvenile osteoporosis [ref 1](#)

imaging [ref 1](#)  
immune deficiency [ref 1](#)  
immune diversity [ref 1](#), [ref 2](#)  
immune dysregulation diseases [ref 1](#)  
immune system [ref 1](#)  
    adaptive immunity [ref 1](#)  
    antibodies [ref 1](#)  
    antigen recognition [ref 1](#)  
    cellular origin and components [ref 1](#)  
    chemokines [ref 1](#)  
    complement [ref 1](#), [ref 2](#)  
    cytokines [ref 1](#), [ref 2](#)  
    haematopoietic stem cells [ref 1](#)  
    innate immunity [ref 1](#)  
    lymphoid organs [ref 1](#)  
    self-tolerance [ref 1](#)  
    T- and B-cells [ref 1](#), [ref 2](#)

immune thrombocytopenic purpura [ref 1](#)  
immune-modulating agents [ref 1](#)  
immunization [ref 1](#)  
    contraindications [ref 1](#)  
    schedule [ref 1](#)  
immunization reactions [ref 1](#)  
immunodeficiency [ref 1](#)  
    categories [ref 1](#)  
    combined [ref 1](#), [ref 2](#)  
    diagnosis [ref 1](#), [ref 2](#)  
    history and examination [ref 1](#)

- non-infective manifestations [ref 1](#)
- patterns of infection [ref 1](#)
- immunodeficiency syndromes [ref 1](#)
- immunoglobulins [ref 1](#)
  - deficiencies [ref 1](#)
- immunoglobulin A deficiency [ref 1](#)
- immunoglobulin A nephropathy [ref 1](#)
- immunological memory [ref 1](#)
- immunology [ref 1](#)
  - antibody deficiencies [ref 1](#)
  - combined immunodeficiency [ref 1](#), [ref 2](#)
  - complement deficiency [ref 1](#)
  - defects of interferon- $\gamma$ /interleukin-12 axis [ref 1](#)
  - host-pathogen interaction [ref 1](#)
  - hypersensitivity reactions [ref 1](#)
  - immune system [ref 1](#)
  - immunodeficiency syndromes [ref 1](#)
  - immunoglobulins [ref 1](#)
  - immunosuppressants and immune-modulating agents [ref 1](#)
  - phagocytic disorders [ref 1](#)
  - routine vaccination in immunosuppressed patients [ref 1](#)
- immunosuppressants [ref 1](#)
- imperforate anus [ref 1](#)
- impetigo [ref 1](#)
- immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) [ref 1](#)
- inadequate airway protection [ref 1](#)
- incontinentia pigmenti [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#), [ref 5](#)
- indirect antiglobulin test [ref 1](#)
- infantile acropustulosis [ref 1](#)
- infantile cardiac outlines [ref 1](#)
- infantile seborrhoeic dermatitis [ref 1](#)
- infections
  - bone and joint [ref 1](#)
  - central nervous system [ref 1](#)
  - congenital [ref 1](#)
  - eyelid [ref 1](#)
  - fungal [ref 1](#)
  - mycobacterial [ref 1](#)
  - neonatal [ref 1](#)
  - orthopaedics [ref 1](#)
  - parasitic [ref 1](#)
  - recurrent [ref 1](#)
  - respiratory system [ref 1](#)
  - urinary tract [ref 1](#)
  - viral [ref 1](#)

- infectious arthritis [ref 1](#)
- infectious diseases [ref 1](#)
  - congenital infections [ref 1](#)
  - differential diagnosis [ref 1](#)
  - fever with focus [ref 1](#)
  - fever with no focus/prolonged fever [ref 1](#)
  - fungal infections [ref 1](#)
  - mycobacterial infections [ref 1](#)
  - new and emerging infections [ref 1](#)
  - notification of [ref 1](#)
  - parasitic infections [ref 1](#)
  - pathogenesis of infection [ref 1](#)
  - tropical diseases [ref 1](#)
  - viral infections [ref 1](#)
- inflammatory bowel disease [ref 1](#)
  - and arthritis [ref 1](#)
- infliximab [ref 1](#)
- inguinal hernia [ref 1](#)
- inhaled foreign body [ref 1](#)
- inheritance [ref 1](#)
- inhibin [ref 1](#)
- innate immunity [ref 1](#)
- inositol triphosphate system [ref 1](#)
- inotropes [ref 1](#)
  - adrenaline [ref 1](#)
  - dobutamine [ref 1](#)
  - dopamine [ref 1](#)
  - milrinone [ref 1](#)
  - noradrenaline [ref 1](#)
- insulin [ref 1](#)
  - administration [ref 1](#), [ref 2](#)
- intention-to-treat analysis [ref 1](#)
- interferons [ref 1](#)
- interquartile range [ref 1](#)
- intersex disorders [ref 1](#)
  - see also* ambiguous genitalia
- interstitial lung diseases of childhood [ref 1](#)
- intestinal atresia [ref 1](#)
- intestinal failure [ref 1](#)
- intestinal lymphangiectasia [ref 1](#)
- intracellular receptors [ref 1](#)
- intrauterine growth retardation [ref 1](#)
- intravenous drugs [ref 1](#)
  - maintenance [ref 1](#)
  - monitoring [ref 1](#)

- intravenous urography [ref 1](#)
- intussusception [ref 1](#), [ref 2](#)
- ionization [ref 1](#)
- iridocyclitis [ref 1](#)
- iris
  - coloboma [ref 1](#)
  - heterochromia irides [ref 1](#)
  - inflammation [ref 1](#)
- iritis [ref 1](#)
- iron
  - nutritional requirement [ref 1](#)
  - poisoning [ref 1](#)
- iron deficiency anaemia [ref 1](#)
- irritable hip [ref 1](#), [ref 2](#)
- isomerism [ref 1](#)
- isovaleric acidaemia [ref 1](#)

jaundice, neonatal [ref 1](#), [ref 2](#)

- approach to [ref 1](#)
- bilirubin metabolism [ref 1](#)
- breast-milk [ref 1](#)
- causes [ref 1](#)
- conjugated hyperbilirubinaemia [ref 1](#)
- haemolysis [ref 1](#)
- physiological [ref 1](#), [ref 2](#)
- prolonged [ref 1](#)
- unconjugated hyperbilirubinaemia [ref 1](#)
- treatment [ref 1](#)

jejunoileal atresia [ref 1](#)

Job's syndrome [ref 1](#)

jugular venous pressure [ref 1](#)

justice [ref 1](#)

juvenile dermatomyositis [ref 1](#)

juvenile idiopathic arthritis [ref 1](#)

juvenile polyps [ref 1](#)

juvenile sarcoidosis [ref 1](#)

Kaletra [ref 1](#)

Kasabach-Merritt syndrome [ref 1](#)

Kawasaki disease [ref 1](#), [ref 2](#), [ref 3](#)

Kearns-Sayre syndrome [ref 1](#)

keloids [ref 1](#)

keratitis [ref 1](#)

keratoconus [ref 1](#)

ketotic hypoglycaemia [ref 1](#)



KID syndrome [ref 1](#)  
kidney  
    congenital abnormalities [ref 1](#)  
    duplex [ref 1](#)  
    horseshoe [ref 1](#)  
    multicystic dysplastic [ref 1](#)  
    *see also* renal  
kinky hair syndrome *see* Menkes disease  
Klinefelter syndrome [ref 1](#), [ref 2](#)  
Klumpke's paralysis [ref 1](#)  
Koebner phenomenon [ref 1](#)  
koilonychia [ref 1](#)  
Krabbe disease [ref 1](#)  
Kruskal-Wallis ANOVA [ref 1](#)  
kuru [ref 1](#)  
kyphosis [ref 1](#)  
  
lacrimal system disorders [ref 1](#)  
    congenital nasolacrimal sac dilatation [ref 1](#)  
    dacryocystitis [ref 1](#)  
    dry eye [ref 1](#)  
    stenosis/obstruction of nasolacrimal duct [ref 1](#)  
    watering eye [ref 1](#)  
lactate [ref 1](#)  
lactose [ref 1](#)  
    intolerance [ref 1](#)  
lamellar ichthyoses [ref 1](#)  
lamivudine [ref 1](#)  
lamotrigine [ref 1](#)  
Langerhans cell histiocytosis [ref 1](#), [ref 2](#)  
Larsen syndrome [ref 1](#)  
laryngeal cleft [ref 1](#), [ref 2](#)  
laryngeal web [ref 1](#)  
laryngomalacia [ref 1](#)  
larynx [ref 1](#)  
Laurence-Moon-Biedl syndrome [ref 1](#)  
laxatives [ref 1](#)  
lead poisoning [ref 1](#)  
learning disability [ref 1](#)  
Leber's hereditary optic neuropathy [ref 1](#)  
Legg-Calvé-Perthes disease [ref 1](#)  
Leigh disease [ref 1](#), [ref 2](#)  
leishmaniasis [ref 1](#)  
lens anomalies [ref 1](#)  
leptospirosis [ref 1](#)

Lesch-Nyhan syndrome [ref 1](#), [ref 2](#)  
leukaemia [ref 1](#)  
    acute lymphoblastic [ref 1](#)  
    acute myeloid [ref 1](#)  
leukocoria [ref 1](#)  
leukocyte adhesion deficiency [ref 1](#)  
leukodystrophies [ref 1](#)  
leukonychia [ref 1](#)  
levetiracetam [ref 1](#)  
lichen planus [ref 1](#), [ref 2](#)  
lichen simplex chronicus [ref 1](#)  
Liddle syndrome [ref 1](#)  
life-sustaining treatment, withholding or withdrawing [ref 1](#)  
    decision-making [ref 1](#)  
    disputes and dissent [ref 1](#)  
    disputes/dissent [ref 1](#)  
    extremely premature infants [ref 1](#)  
    legal framework [ref 1](#)  
    professional guidance [ref 1](#)  
lightning injury [ref 1](#)  
likelihood ratios [ref 1](#)  
limb pains, non-organic [ref 1](#)  
limb-girdle muscular dystrophy [ref 1](#)  
limbal dermoid [ref 1](#)  
linear regression [ref 1](#)  
lipid disorders [ref 1](#)  
lipogenesis [ref 1](#)  
lipolysis [ref 1](#)  
Lisch nodules [ref 1](#)  
lissencephaly [ref 1](#)  
*Listeria monocytogenes* [ref 1](#)  
listeriosis [ref 1](#)  
live vaccines [ref 1](#)  
liver, drugs and [ref 1](#)  
liver disease [ref 1](#)  
    chronic [ref 1](#)  
        autoimmune hepatitis [ref 1](#)  
        causes [ref 1](#)  
        chronic viral hepatitis [ref 1](#)  
        liver transplantation [ref 1](#)  
        non-alcoholic fatty liver disease [ref 1](#)  
        portal hypertension [ref 1](#), [ref 2](#)  
    drug-induced [ref 1](#)  
    total parenteral nutrition-induced [ref 1](#)  
liver failure

acute [ref 1](#)

causes [ref 1](#)

paracetamol poisoning [ref 1](#)

Wilson disease [ref 1](#)

end-stage [ref 1](#)

liver function tests [ref 1](#)

liver phosphorylase deficiency [ref 1](#)

liver transplantation [ref 1](#)

lobar emphysema, congenital [ref 1](#)

lobar sequestration [ref 1](#)

long-bone fracture [ref 1](#)

long-chain defects [ref 1](#)

loop of Henle [ref 1](#), [ref 2](#)

loose anagen syndrome [ref 1](#)

low-density lipoprotein [ref 1](#)

low-renin hypertension [ref 1](#)

Lown-Ganong-Levine syndrome [ref 1](#)

lumbar puncture [ref 1](#)

lung disease

chronic [ref 1](#)

congenital [ref 1](#)

environmental influences [ref 1](#)

lung function testing [ref 1](#)

lung transplantation [ref 1](#)

luteinizing hormone [ref 1](#)

Lyme disease [ref 1](#)

lymphocytes [ref 1](#), [ref 2](#)

lymphocytic interstitial pneumonitis [ref 1](#), [ref 2](#)

lymphocytosis [ref 1](#)

lymphoid organs [ref 1](#)

lyonization [ref 1](#)

McArdle disease [ref 1](#)

macrocephaly [ref 1](#)

macroglossia [ref 1](#)

macrophages [ref 1](#)

MAG-3 scan [ref 1](#)

magnesium [ref 1](#)

magnetic resonance imaging [ref 1](#), [ref 2](#)

magnetic resonance urography [ref 1](#)

major histocompatibility complex *see* MHC

malabsorption [ref 1](#)

malacias [ref 1](#)

malaria [ref 1](#)

malignancy [ref 1](#)

bone marrow transplantation [ref 1](#)

bone tumours [ref 1](#)

brain tumours [ref 1](#)

environmental factors predisposing to [ref 1](#)

germ-cell tumours [ref 1](#)

haemophagocytic lymphohistiocytosis [ref 1](#)

hepatoblastoma [ref 1](#)

Langerhans cell histiocytosis [ref 1](#)

late effects of treatment [ref 1](#)

leukaemia [ref 1](#)

lymphoma [ref 1](#)

management [ref 1](#)

neuroblastoma [ref 1](#)

palliative care [ref 1](#)

retinoblastoma [ref 1](#)

soft-tissue sarcomas [ref 1](#)

syndromes/conditions predisposing to [ref 1](#)

tumour-lysis syndrome [ref 1](#)

Wilms' tumour [ref 1](#)

malnutrition [ref 1](#)

malrotation [ref 1](#), [ref 2](#)

manganese, abnormalities [ref 1](#)

Mann-Whitney U-test [ref 1](#)

Mantoux test [ref 1](#)

maple syrup urine disease [ref 1](#)

marasmus [ref 1](#)

Marcus Gunn jaw-winking syndrome [ref 1](#)

Marfan syndrome [ref 1](#), [ref 2](#), [ref 3](#)

mastoiditis [ref 1](#)

maternal engraftment [ref 1](#)

mean [ref 1](#)

measles [ref 1](#)

mechanical ventilation [ref 1](#)

Meckel's diverticulum [ref 1](#), [ref 2](#)

meconium aspiration syndrome [ref 1](#)

meconium ileus [ref 1](#), [ref 2](#)

median [ref 1](#), [ref 2](#)

medium-chain acyl-CoA dehydrogenase deficiency [ref 1](#)

medulloblastoma [ref 1](#), [ref 2](#), [ref 3](#)

megacystis-microcolon-intestinal hypoperistalsis syndrome [ref 1](#)

meiosis [ref 1](#)

melanocytic naevi [ref 1](#)

MELAS [ref 1](#), [ref 2](#)

memory cells [ref 1](#)

mendelian inheritance

autosomal dominant conditions [ref 1](#)

autosomal recessive conditions [ref 1](#)

pedigree diagrams [ref 1](#)

X-linked dominant conditions [ref 1](#)

X-linked recessive conditions [ref 1](#)

meningitis [ref 1](#), [ref 2](#)

bacterial [ref 1](#)

neonatal [ref 1](#)

tuberculous [ref 1](#)

meningitis C vaccine [ref 1](#)

meningocele [ref 1](#)

meningomyelocele [ref 1](#)

Menkes disease [ref 1](#), [ref 2](#), [ref 3](#)

mental health [ref 1](#)

merosin-negative congenital muscular dystrophy [ref 1](#)

merosin-positive congenital muscular dystrophy [ref 1](#)

MERRF [ref 1](#), [ref 2](#)

metabolic acidosis [ref 1](#), [ref 2](#), [ref 3](#)

metabolic alkalosis [ref 1](#), [ref 2](#)

metabolic disorders, ocular manifestations [ref 1](#)

metabolic medicine [ref 1](#)

abetalipoproteinaemia [ref 1](#), [ref 2](#)

acute management [ref 1](#)

approach to metabolic case [ref 1](#)

basic metabolism [ref 1](#)

carbohydrate metabolism disorders [ref 1](#)

fat oxidation disorders [ref 1](#)

lipid disorders [ref 1](#)

long-term management [ref 1](#)

mitochondrial disorders [ref 1](#)

mucopolysaccharidoses [ref 1](#)

organic acidaemias [ref 1](#)

peroxisomal disorders [ref 1](#)

presentation [ref 1](#)

screening [ref 1](#)

sphingolipidoses [ref 1](#)

urea cycle defects [ref 1](#)

metabolic metabolism, amino acid metabolism disorders [ref 1](#)

metachromic leukodystrophy [ref 1](#), [ref 2](#)

metal-induced hyperpigmentation [ref 1](#)

metaphyseal fractures [ref 1](#)

methylmalonic acidaemia [ref 1](#)

methylparaben [ref 1](#)

methylphenidate (Ritalin) [ref 1](#)

MHC class I [ref 1](#)

MHC class II [ref 1](#)  
microangiopathic haemolytic anaemia [ref 1](#)  
microcephaly [ref 1](#), [ref 2](#)  
microcornea [ref 1](#)  
microdeletion syndromes [ref 1](#)  
micturating cystourethrogram [ref 1](#)  
mid-parental height [ref 1](#)  
migraine [ref 1](#)  
miliaria [ref 1](#)  
milrinone [ref 1](#)  
mineralocorticoids [ref 1](#)  
miosis [ref 1](#)  
mitochondrial disease [ref 1](#)  
mitochondrial disorders [ref 1](#), [ref 2](#)  
mitosis [ref 1](#)  
MMR vaccine [ref 1](#), [ref 2](#)  
Moebius syndrome [ref 1](#)  
molecular genetics [ref 1](#)  
molluscum contagiosum [ref 1](#), [ref 2](#)  
molybdenum, abnormalities [ref 1](#)  
Mongolian blue spots [ref 1](#), [ref 2](#)  
monocytes [ref 1](#), [ref 2](#)  
monosaccharide absorption disorders [ref 1](#)  
monosomy [ref 1](#)  
Monro-Kellie doctrine [ref 1](#)  
moral conflicts for doctors [ref 1](#)  
moral duties of doctors [ref 1](#)  
moral status of children [ref 1](#)  
motilin [ref 1](#)  
movement disorders  
    ataxia [ref 1](#)  
    cerebral palsy [ref 1](#)  
    dystonia [ref 1](#)  
    tics and Tourette syndrome [ref 1](#)  
mucopolysaccharidoses [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#)  
multicystic dysplastic kidney [ref 1](#)  
multiple endocrine neoplasia syndromes [ref 1](#)  
multiple sulphatase deficiency [ref 1](#)  
multiplex ligation-dependent probe amplification [ref 1](#)  
mumps [ref 1](#)  
Munchausen syndrome by proxy [ref 1](#)  
muscle phosphorylase deficiency [ref 1](#)  
myalgic encephalopathy *see* chronic fatigue syndrome  
myasthenia gravis [ref 1](#), [ref 2](#), [ref 3](#)  
    and fetal malformations [ref 1](#)

maternal, effects on fetus and newborn [ref 1](#)  
mycobacterial infections [ref 1](#)  
mycophenolate mofetil [ref 1](#)  
mydriasis [ref 1](#)  
myelomeningocele [ref 1](#)  
mycoplasma encephalitis [ref 1](#)  
myoglobinuria [ref 1](#)  
myopathies [ref 1](#), [ref 2](#)  
myopia [ref 1](#)  
myotonia congenita [ref 1](#), [ref 2](#)  
myotonic dystrophy [ref 1](#), [ref 2](#)

naevus flammeus [ref 1](#)  
nail-patella syndrome [ref 1](#)  
nails [ref 1](#)  
nappy rash [ref 1](#)  
nasal polyps [ref 1](#)  
nasogastric tube feeding [ref 1](#)  
nasojejunal feeding [ref 1](#)  
National Health Service Litigation Authority (NHSLA) [ref 1](#)  
National Health Service trusts [ref 1](#)  
National Institute for Clinical Excellence (NICE) [ref 1](#)  
National Patient Safety Agency (NPSA) [ref 1](#)  
National Reporting and Learning Service (NRLS) [ref 1](#)  
necrotizing enterocolitis [ref 1](#), [ref 2](#)  
neglect [ref 1](#)  
neonatal cardiac outlines [ref 1](#)  
neonatal conjunctivitis [ref 1](#)  
neonatal erythroderma [ref 1](#)  
neonatal isoimmune thrombocytopenia [ref 1](#)  
neonatal jaundice [ref 1](#)  
neonatal lupus [ref 1](#)  
neonatal lupus erythematosus [ref 1](#)  
neonatal mortality rate [ref 1](#)  
neonatal surgery [ref 1](#)  
neonatal thyrotoxicosis [ref 1](#)  
neonatal tumours [ref 1](#)  
neonate  
absorption [ref 1](#)  
body composition [ref 1](#)  
cardiovascular problems [ref 1](#)  
endocrine problems [ref 1](#)  
fluid and nutritional requirements [ref 1](#)  
gastroenterology and nutrition [ref 1](#)  
genitourinary problems [ref 1](#)

haematology/coagulation problems [ref 1](#)

idiopathic hepatitis [ref 1](#)

infection [ref 1](#)

    bacterial [ref 1](#)

    congenital viral infection [ref 1](#)

    fungal and protozoal infection [ref 1](#)

intestinal obstruction [ref 1](#)

neurological problems [ref 1](#)

    hypotonia [ref 1](#)

    neonatal encephalopathy [ref 1](#)

    neonatal seizures [ref 1](#)

    peri-intraventricular haemorrhage [ref 1](#)

    periventricular leukomalacia [ref 1](#)

    retinopathy of prematurity [ref 1](#)

neurology [ref 1](#)

parenteral nutrition [ref 1](#)

persistent pulmonary hypertension [ref 1](#)

prematurity [ref 1](#)

renal function [ref 1](#)

respiratory problems [ref 1](#)

    chest wall abnormalities [ref 1](#)

    chronic lung disease [ref 1](#)

    congenital lung problems [ref 1](#)

    extracorporeal membrane oxygenation [ref 1](#)

    mechanical ventilation [ref 1](#)

    meconium aspiration syndrome [ref 1](#)

    pneumonia [ref 1](#)

    pulmonary air leak [ref 1](#)

    surfactant deficiency [ref 1](#)

    upper airway obstruction [ref 1](#)

skin disorders [ref 1](#)

nephrocalcinosis [ref 1](#)

nephrolithiasis [ref 1](#)

nephrology [ref 1](#)

    acid-base, fluid and electrolytes [ref 1](#)

    acute kidney injury [ref 1](#)

    chronic renal failure [ref 1](#)

    embryology [ref 1](#)

    fetal and neonatal renal function [ref 1](#)

    glomerulonephritis [ref 1](#)

    hypertension [ref 1](#)

    inherited diseases [ref 1](#)

    investigations [ref 1](#)

    nocturnal enuresis [ref 1](#)

    physiology [ref 1](#)



- renal tubulopathies [ref 1](#)
- urinary tract infection [ref 1](#)
- urological abnormalities [ref 1](#)

nephronophthisis [ref 1](#)

nephrotic syndrome [ref 1](#)

- clinical features [ref 1](#)

- complications [ref 1](#)

- congenital [ref 1](#)

- definitions [ref 1](#)

- treatment [ref 1](#)

nervous system

- developmental abnormalities [ref 1](#)

- normal development [ref 1](#)

Netherton's syndrome [ref 1](#)

neural tube defects [ref 1](#), [ref 2](#)

neuro-oncology [ref 1](#)

neuroblastoma [ref 1](#)

neurocutaneous syndromes [ref 1](#)

neurofibromatosis [ref 1](#), [ref 2](#), [ref 3](#)

neurohypophysis [ref 1](#)

neurological problems of newborn [ref 1](#)

neurometabolic diseases [ref 1](#)

- abnormalities of copper metabolism [ref 1](#)

- amino and organic acid disorders [ref 1](#)

- leukodystrophies [ref 1](#)

- mitochondrial disease [ref 1](#)

- neurotransmitter and urea cycle disorders [ref 1](#)

- storage disorders [ref 1](#)

neuromuscular disorders [ref 1](#)

- acute [ref 1](#)

- anterior horn cell disease [ref 1](#)

- arthrogrypotic syndromes [ref 1](#)

- floppy infant [ref 1](#)

- muscular dystrophies [ref 1](#)

- myopathies [ref 1](#), [ref 2](#)

- neuromuscular junction disorders [ref 1](#)

- neuropathies [ref 1](#)

- respiratory system [ref 1](#)

- spina bifida [ref 1](#)

neuromuscular junction disorders [ref 1](#)

neuronal ceroid-lipofuscinoses [ref 1](#)

neuropathic bladder [ref 1](#)

neuropathies [ref 1](#)

neurotransmitter disorders [ref 1](#)

neutral-lipid storage disease [ref 1](#)

neutropenia [ref 1](#)  
    congenital [ref 1](#)  
    cyclical [ref 1](#)  
neutrophilia [ref 1](#)  
neutrophils [ref 1](#), [ref 2](#), [ref 3](#)  
nevirapine [ref 1](#)  
Niemann-Pick disease [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#)  
nifedipine [ref 1](#)  
night terrors [ref 1](#)  
nightmares [ref 1](#), [ref 2](#)  
nitric oxide [ref 1](#), [ref 2](#)  
nocturnal enuresis [ref 1](#)  
non-accidental injury [ref 1](#)  
non-alcoholic fatty liver disease [ref 1](#)  
non-bullous ichthyosiform erythroderma [ref 1](#)  
non-Hodgkin lymphoma [ref 1](#)  
non-ketotic hyperglycinaemia [ref 1](#), [ref 2](#)  
non-maleficence [ref 1](#)  
Noonan syndrome [ref 1](#), [ref 2](#)  
noradrenaline [ref 1](#)  
normal distribution [ref 1](#)  
Norwood operation [ref 1](#)  
nose and sinuses [ref 1](#)  
nuchal translucency [ref 1](#)  
null hypothesis [ref 1](#)  
number needed to treat [ref 1](#)  
nutrition  
    breast-feeding [ref 1](#)  
    fat-soluble vitamins [ref 1](#)  
    folate [ref 1](#)  
    iron [ref 1](#)  
    nutritional assessment [ref 1](#)  
    nutritional requirements [ref 1](#)  
    vitamin B<sub>12</sub> [ref 1](#)  
    zinc [ref 1](#)  
nutritional impairment [ref 1](#)  
nutritional management [ref 1](#)  
nutritional supplementation [ref 1](#)  
nystagmus [ref 1](#), [ref 2](#)  
    vertical [ref 1](#)  
  
obesity [ref 1](#)  
    assessment [ref 1](#)  
    causes [ref 1](#)  
    consequences [ref 1](#)

constitutional [ref 1](#)  
management [ref 1](#)  
obliterative bronchiolitis [ref 1](#)  
observational studies [ref 1](#)  
ocular albinism [ref 1](#)  
ocular coherence tomography [ref 1](#)  
ocular trauma [ref 1](#)  
oculocutaneous albinism [ref 1](#)  
odds ratio [ref 1](#), [ref 2](#)  
oesophageal atresia [ref 1](#), [ref 2](#)  
oesophageal foreign bodies [ref 1](#)  
oesophagus [ref 1](#)  
oestrogen [ref 1](#)  
OKT3 [ref 1](#)  
oligaemic lung fields [ref 1](#)  
oligohydramnios [ref 1](#)  
Omenn syndrome [ref 1](#)  
ophthalmological investigations [ref 1](#)  
ophthalmology [ref 1](#)  
    amblyopia [ref 1](#)  
    anatomy [ref 1](#)  
    conjunctiva [ref 1](#)  
    cornea [ref 1](#)  
    eye examination [ref 1](#)  
    eyelid abnormalities [ref 1](#)  
    iris inflammation [ref 1](#)  
    lacrimal system disorders [ref 1](#)  
    lens anomalies [ref 1](#)  
    metabolic disorders [ref 1](#)  
    ocular trauma [ref 1](#)  
    optic nerve disorders [ref 1](#)  
    painful red eye [ref 1](#)  
    pupil anomalies [ref 1](#)  
    retinal anomalies [ref 1](#)  
    sclera [ref 1](#)  
    uveal tract disorders [ref 1](#)  
    visual impairment [ref 1](#)  
ophthalmoplegia  
    acquired [ref 1](#)  
    congenital [ref 1](#)  
opiate abuse, maternal [ref 1](#)  
optic atrophy [ref 1](#)  
optic disc coloboma [ref 1](#)  
optic glioma [ref 1](#)  
optic nerve disorders [ref 1](#)

oral rehydration solution [ref 1](#)  
orbital infections [ref 1](#)  
    orbital cellulitis [ref 1](#)  
    preseptal cellulitis [ref 1](#)  
orbital tumours [ref 1](#)  
organic acidaemias [ref 1](#)  
organic acids [ref 1](#)  
oropharyngeal incoordination [ref 1](#)  
orthopaedics [ref 1](#)  
    embryology [ref 1](#)  
    infection [ref 1](#)  
    lower limb [ref 1](#)  
    metabolic disorders [ref 1](#)  
    neuromuscular disorders [ref 1](#)  
    spine [ref 1](#)  
    trauma [ref 1](#)  
    upper limb [ref 1](#)  
osmoregulation [ref 1](#)  
osmotic equilibrium [ref 1](#)  
osteogenesis imperfecta [ref 1](#), [ref 2](#)  
osteomalacia [ref 1](#)  
osteomyelitis [ref 1](#), [ref 2](#)  
osteopetrosis [ref 1](#)  
osteoporosis [ref 1](#)  
    idiopathic juvenile [ref 1](#)  
osteosarcoma [ref 1](#)  
otitis media [ref 1](#)  
otoacoustic emissions test [ref 1](#)  
outcome measurements [ref 1](#)  
overlap syndrome [ref 1](#)  
oxazolidinones [ref 1](#)  
oxcarbazepine [ref 1](#)  
oxygen therapy [ref 1](#)  
    emergency [ref 1](#)  
oxygen-dissociation curve [ref 1](#)  
oxytocin [ref 1](#)  
  
*p*-value [ref 1](#)  
16p11.2 microdeletion syndrome [ref 1](#)  
pachygyria [ref 1](#)  
pachyonychia congenita [ref 1](#)  
paediatric dosing [ref 1](#)  
palliative care [ref 1](#)  
palpation [ref 1](#)  
pancreas [ref 1](#), [ref 2](#)

- acute pancreatitis [ref 1](#)
- chronic pancreatitis [ref 1](#)
- function [ref 1](#)
- pancreatic polypeptide [ref 1](#)
- panhypogammaglobulinaemia [ref 1](#)
- panhypopituitarism [ref 1](#), [ref 2](#)
- papilloedema [ref 1](#)
- papillomatosis [ref 1](#)
- paracetamol
  - absorption and  $pK_a$  [ref 1](#)
- poisoning [ref 1](#), [ref 2](#)
- parakeratosis pustulosa [ref 1](#)
- paramyotonia congenita [ref 1](#)
- parapneumonic effusions [ref 1](#)
- parasitic infections [ref 1](#)
- parathyroid hormone [ref 1](#)
- paratyphoid [ref 1](#)
- parenteral nutrition
  - neonate [ref 1](#)
  - see also* total parenteral nutrition
- parents, responsibilities, rights, duties and powers [ref 1](#), [ref 2](#)
- paronychia [ref 1](#)
- parvovirus B19 [ref 1](#)
  - congenital [ref 1](#), [ref 2](#)
- Patau syndrome [ref 1](#), [ref 2](#), [ref 3](#)
- patent ductus arteriosus [ref 1](#)
- Patient Advocacy and Liaison Services (PALS) [ref 1](#)
- patient experience [ref 1](#)
- patient safety [ref 1](#)
- PCT *see* polymerase chain reaction
- peanut allergy [ref 1](#)
- pectus carinatum [ref 1](#)
- pediculosis [ref 1](#)
- pediculosis capitis [ref 1](#)
- pedigree diagrams [ref 1](#)
- pelviureteric junction obstruction [ref 1](#)
- pemphigus [ref 1](#)
- penicillin, absorption and  $pK_a$  [ref 1](#)
- pentalogy of Cantrell [ref 1](#), [ref 2](#)
- peptic ulcer disease [ref 1](#)
- peri-intraventricular haemorrhage [ref 1](#)
- perianal streptococcal infection [ref 1](#)
- perianal warts [ref 1](#)
- pericarditis [ref 1](#)
- perinatal mortality rate [ref 1](#)

peripheral neurophysiology [ref 1](#)  
periventricular heterotopia [ref 1](#)  
periventricular leukomalacia [ref 1](#), [ref 2](#)  
periventricular-intraventricular haemorrhage [ref 1](#)  
peroxisomal disorders [ref 1](#), [ref 2](#)  
persistent arterial duct [ref 1](#)  
persistent ductus arteriosus [ref 1](#)  
persistent fetal circulation [ref 1](#)  
persistent pulmonary hypertension of newborn [ref 1](#)  
Perthes disease [ref 1](#)  
pertussis [ref 1](#)  
pertussis vaccine [ref 1](#), [ref 2](#)  
pes excavatum [ref 1](#)  
Peutz-Jeghers syndrome [ref 1](#)  
PHACES syndrome [ref 1](#)  
phaeochromocytoma [ref 1](#), [ref 2](#)  
phagocytes [ref 1](#), [ref 2](#)  
phagocytic disorders [ref 1](#)  
pharmacodynamics [ref 1](#)  
pharmacokinetics [ref 1](#)  
phenylketonuria [ref 1](#), [ref 2](#)  
    and fetal malformations [ref 1](#)  
phenytoin [ref 1](#)  
    absorption and  $pK_a$  [ref 1](#)  
phimosis [ref 1](#)  
photosensitive disorders [ref 1](#)  
phosphate [ref 1](#)  
phosphofructokinase deficiency [ref 1](#)  
phosphorylase-b-kinase deficiency [ref 1](#)  
photophobia [ref 1](#)  
phototherapy [ref 1](#)  
physical abuse [ref 1](#)  
    examination [ref 1](#)  
    history taking [ref 1](#)  
    investigation [ref 1](#)  
    management [ref 1](#)  
    predisposing factors [ref 1](#)  
    specific presentations [ref 1](#)  
    types of injuries [ref 1](#)  
PIBIDS [ref 1](#)  
pica [ref 1](#)  
Pierre Robin syndrome [ref 1](#), [ref 2](#)  
pigmentation disorders [ref 1](#)  
    café-au-lait macules [ref 1](#)  
    hyperpigmentation [ref 1](#)

- hypopigmentation [ref 1](#)
- tuberous sclerosis [ref 1](#)
- pimecrolimus [ref 1](#)
- pituitary gland
  - anatomy [ref 1](#)
  - anterior
    - disorders of [ref 1](#)
    - hormones of [ref 1](#)
    - stimulation tests [ref 1](#)
    - treatment of deficiencies [ref 1](#)
  - combined pituitary function test [ref 1](#)
  - disorders of [ref 1](#)
  - panhypopituitarism [ref 1](#)
  - posterior
    - disorders of [ref 1](#)
    - function tests [ref 1](#)
    - treatment of deficiencies [ref 1](#)
- pityriasis lichenoides chronica [ref 1](#)
- pityriasis rosea [ref 1](#)
- pityriasis rubra pilaris [ref 1](#)
- pityriasis versicolor [ref 1](#)
- pK<sub>a</sub> [ref 1](#)
- placental physiology [ref 1](#)
- plasma cells [ref 1](#), [ref 2](#)
- platelets [ref 1](#)
  - functional abnormalities [ref 1](#)
- plethoric lung fields [ref 1](#)
- pneumococcal vaccine [ref 1](#)
- Pneumocystic jiroveci* pneumonia [ref 1](#)
- pneumomediastinum [ref 1](#)
- pneumonia [ref 1](#)
  - bacterial [ref 1](#)
  - Pneumocystic jiroveci* [ref 1](#)
  - viral [ref 1](#)
- pneumothorax [ref 1](#), [ref 2](#)
- poisoning [ref 1](#)
- poisoning *see* toxicology
- Poland syndrome [ref 1](#)
- police protection [ref 1](#)
- polio vaccine [ref 1](#), [ref 2](#)
- polyarteritis nodosa [ref 1](#)
- polycystic kidney disease [ref 1](#)
- polycythaemia [ref 1](#), [ref 2](#)
- polydipsia [ref 1](#)
- polyhydramnios [ref 1](#)

polymerase chain reaction [ref 1](#)  
polymicrogyria [ref 1](#)  
polyposis [ref 1](#)  
polysorbate [ref 1](#)  
polysplenia syndrome [ref 1](#), [ref 2](#)  
polyuria [ref 1](#)  
Pompe disease [ref 1](#), [ref 2](#)  
porphyria [ref 1](#), [ref 2](#), [ref 3](#)  
port wine stain [ref 1](#)  
portal hypertension [ref 1](#), [ref 2](#)  
portopulmonary hypertension [ref 1](#)  
positron emission tomography [ref 1](#)  
post-enteritis syndrome [ref 1](#)  
posterior fossa tumours [ref 1](#)  
posterior urethral valves [ref 1](#)  
Potter sequence [ref 1](#)  
Prader-Willi syndrome [ref 1](#), [ref 2](#)  
preauricular pits [ref 1](#)  
precocious puberty [ref 1](#)  
precordium, examination of [ref 1](#)  
prednisolone [ref 1](#)  
pregnancy, drugs in [ref 1](#)  
preimplantation genetic diagnosis [ref 1](#)  
prematurity [ref 1](#)  
    incidence and causes [ref 1](#)  
    mortality [ref 1](#)  
    outcome [ref 1](#)  
    small-for-gestational-age babies [ref 1](#)  
prenatal testing [ref 1](#)  
prescribing outside licence [ref 1](#)  
progesterone [ref 1](#)  
progressive familial intrahepatic cholestasis [ref 1](#)  
prolactin [ref 1](#), [ref 2](#)  
propionic acidaemia [ref 1](#)  
proptosis [ref 1](#)  
    orbital infections [ref 1](#)  
    orbital tumours [ref 1](#)  
propylene glycol [ref 1](#)  
prostacyclin [ref 1](#)  
protein metabolism [ref 1](#)  
protein-energy malnutrition [ref 1](#)  
protein-losing enteropathy [ref 1](#)  
proteins, digestion [ref 1](#)  
proteinuria [ref 1](#)  
prothrombin time [ref 1](#)



proximal tubule [ref 1](#)  
proximal tubulopathies [ref 1](#)  
prune-belly syndrome [ref 1](#)  
pseudo-Bartter syndrome [ref 1](#)  
pseudohypoaldosteronism [ref 1](#)  
pseudohypoparathyroidism [ref 1](#), [ref 2](#)  
pseudomembranous colitis [ref 1](#)  
*Pseudomonas aeruginosa* [ref 1](#)  
pseudostrabismus [ref 1](#)  
psoriasis [ref 1](#)  
    nail involvement [ref 1](#)  
ptosis [ref 1](#)  
pubertal growth spurt [ref 1](#)  
puberty [ref 1](#)  
    clinical features [ref 1](#)  
    delayed [ref 1](#)  
    discordant [ref 1](#)  
    hormonal control [ref 1](#)  
    physiology [ref 1](#)  
    precocious [ref 1](#)  
    premature thelarche [ref 1](#)  
    Tanner stages [ref 1](#)  
pulmonary air leak [ref 1](#)  
pulmonary artery band [ref 1](#)  
pulmonary atresia [ref 1](#)  
pulmonary hypertension [ref 1](#), [ref 2](#)  
    arterial [ref 1](#)  
    drug therapy [ref 1](#)  
    hypoxemia-related [ref 1](#)  
    increased pulmonary blood flow [ref 1](#)  
    left heart disease [ref 1](#)  
    persistent of newborn [ref 1](#)  
    thromboembolic [ref 1](#)  
pulmonary hypoplasia [ref 1](#)  
pulmonary interstitial emphysema [ref 1](#)  
pulmonary sequestration [ref 1](#)  
pulmonary stenosis [ref 1](#), [ref 2](#)  
pulmonary venous hypertension [ref 1](#), [ref 2](#)  
pulse [ref 1](#)  
pulse oximetry [ref 1](#)  
pulseless electrical activity [ref 1](#)  
pulseless ventricular tachycardia [ref 1](#)  
pupils, unequal [ref 1](#)  
pure-tone audiometry [ref 1](#)  
purine nucleoside phosphorylase deficiency [ref 1](#)

pyloric atresia [ref 1](#)  
pyloric stenosis [ref 1](#)  
pyruvate kinase deficiency [ref 1](#)  
pyruvate metabolism [ref 1](#)

22q11 microdeletion [ref 1](#)  
quantitative fluorescence polymerase chain reaction [ref 1](#)

radionuclear angiography [ref 1](#)  
radiotherapy, effects of [ref 1](#)  
randomization [ref 1](#)  
randomized controlled trials [ref 1](#)  
ranula [ref 1](#)  
rashes [ref 1](#), [ref 2](#)

- atopic eczema [ref 1](#)
- infections and infestations [ref 1](#)
- psoriasis [ref 1](#)
- urticaria [ref 1](#)

Rastelli operation [ref 1](#)  
re-feeding syndrome [ref 1](#)  
re-warming [ref 1](#)  
reactive arthritis [ref 1](#)  
reciprocal translocations [ref 1](#)  
red cells

- enzyme defects [ref 1](#)
- inclusions [ref 1](#)
- physiology [ref 1](#)
- transfusion [ref 1](#)
- transfusions [ref 1](#)

red eye [ref 1](#)  
reduction division [ref 1](#)  
Reference Nutrient Intake [ref 1](#)  
reflex sympathetic dystrophy [ref 1](#)  
reflux oesophagitis [ref 1](#)  
refractive errors [ref 1](#)  
Refsum's disease [ref 1](#)  
regression analysis [ref 1](#)  
Reiter syndrome [ref 1](#)  
relative risk [ref 1](#)  
renal arteriography [ref 1](#)  
renal biopsy [ref 1](#)  
renal disease [ref 1](#)  
renal excretion [ref 1](#)  
renal failure

- acute *see* acute kidney injury

- chronic [ref 1](#)
- neonatal [ref 1](#)
- renal imaging [ref 1](#)
- renal osteodystrophy [ref 1](#)
- renal pelvis dilatation [ref 1](#)
- renal transplantation [ref 1](#)
- renal tubular physiology [ref 1](#)
- renal tubulopathies [ref 1](#)
  - collecting duct [ref 1](#)
  - distal tubule [ref 1](#)
  - loop of Henle [ref 1](#)
  - proximal tubule [ref 1](#)
- renin [ref 1](#)
- renin-angiotensin-aldosterone system [ref 1](#)
- repetitive behaviour [ref 1](#)
- rescue breaths [ref 1](#)
- research in children [ref 1](#)
- research questions [ref 1](#)
- respiration, control of [ref 1](#)
- respiratory acidosis [ref 1](#)
- respiratory alkalosis [ref 1](#)
- respiratory chain disorders [ref 1](#)
- respiratory failure [ref 1](#), [ref 2](#)
  - apnoea [ref 1](#)
  - asthma [ref 1](#)
  - bronchiolitis [ref 1](#)
  - cardiac causes [ref 1](#)
  - pertussis [ref 1](#)
  - trauma and breathing difficulties [ref 1](#)
  - treatment [ref 1](#)
- respiratory system [ref 1](#)
  - anatomy and physiology [ref 1](#)
  - asthma [ref 1](#)
  - bronchiectasis [ref 1](#)
  - bronchopulmonary dysplasia [ref 1](#)
  - cystic fibrosis [ref 1](#)
  - defence mechanisms [ref 1](#)
  - ear, nose, throat and upper airway [ref 1](#)
  - embryology [ref 1](#)
  - fetal/postnatal lung growth [ref 1](#)
  - infections [ref 1](#)
  - inhaled foreign body [ref 1](#)
  - neuromuscular disorders [ref 1](#)
  - pneumothorax [ref 1](#)
- resuscitation

cardiac arrest [ref 1](#)  
post-resuscitation management [ref 1](#)  
when to stop [ref 1](#)  
retinal anomalies [ref 1](#)  
  albinism [ref 1](#)  
  Coat disease [ref 1](#)  
  coloboma [ref 1](#)  
  detachment [ref 1](#)  
  diabetic retinopathy [ref 1](#)  
  diabetic retinopathy [ref 1](#)  
  hypertensive retinopathy [ref 1](#)  
  myelinated nerve fibres [ref 1](#)  
  sickle cell retinopathy [ref 1](#)  
retinal haemorrhage [ref 1](#)  
retinal infections [ref 1](#)  
retinitis pigmentosa [ref 1](#)  
retinoblastoma [ref 1](#), [ref 2](#)  
retinopathy of prematurity [ref 1](#), [ref 2](#)  
Rett syndrome [ref 1](#)  
revalidation [ref 1](#)  
reverse transcription PCT [ref 1](#)  
rhabdomyosarcoma [ref 1](#)  
rheumatic fever [ref 1](#), [ref 2](#)  
rheumatology [ref 1](#)  
rib fractures [ref 1](#)  
rickets [ref 1](#), [ref 2](#)  
ringworm [ref 1](#)  
risk difference [ref 1](#)  
risk management [ref 1](#)  
risk ratio [ref 1](#)  
risk reporting [ref 1](#)  
risk reporting [ref 1](#)  
rituximab [ref 1](#)  
RNA [ref 1](#)  
Robertsonian translocations [ref 1](#)  
rocker bottom foot [ref 1](#)  
root cause analysis [ref 1](#)  
roseola infantum [ref 1](#)  
Rothmund-Thomson syndrome [ref 1](#), [ref 2](#)  
rubella [ref 1](#), [ref 2](#)  
  congenital [ref 1](#), [ref 2](#)  
  and fetal malformations [ref 1](#)  
  vaccine [ref 1](#), [ref 2](#)  
Rubinstein-Taybi syndrome [ref 1](#)  
Russell-Silver syndrome [ref 1](#)

salbutamol [ref 1](#)  
salmon patch [ref 1](#)  
sample size [ref 1](#)  
Sanfilippo syndrome [ref 1](#)  
sarcoid [ref 1](#)  
sarcoma, soft-tissue [ref 1](#)  
SARS [ref 1](#)  
scabies [ref 1](#)  
scalp scaling [ref 1](#)  
schistosomiasis [ref 1](#)  
schizophrenia [ref 1](#)  
school refusal [ref 1](#)  
school-aged children  
    health surveillance [ref 1](#)  
    school refusal [ref 1](#)  
    sleep problems [ref 1](#)  
Schwachman-Bodian-Diamond syndrome [ref 1](#)  
Schwachman-Diamond syndrome [ref 1](#)  
scimitar syndrome [ref 1](#)  
sclera [ref 1](#)  
scleritis [ref 1](#)  
scleroderma [ref 1](#)  
scoliosis [ref 1](#)  
screening  
    cardiology [ref 1](#)  
    hearing [ref 1](#)  
    metabolic medicine [ref 1](#), [ref 2](#)  
screening tests [ref 1](#)  
scrotal pain [ref 1](#)  
sebaceous naevi [ref 1](#)  
second messengers [ref 1](#)  
secretin [ref 1](#)  
seizures [ref 1](#)  
    anoxic [ref 1](#)  
    neonatal [ref 1](#), [ref 2](#)  
    psychogenic [ref 1](#)  
    *see also* epilepsy  
selective serotonin reuptake inhibitors [ref 1](#)  
selenium, abnormalities [ref 1](#)  
self-harm [ref 1](#)  
self-mutilation [ref 1](#)  
self-poisoning [ref 1](#)  
sepsis [ref 1](#)  
septic arthritis [ref 1](#), [ref 2](#)

septic shock [ref 1](#), [ref 2](#)  
septo-optic dysplasia [ref 1](#)  
sequential segmental arrangement, nomenclature [ref 1](#)  
Serious Incident Requiring Investigation (SIRI) [ref 1](#)  
severe acute respiratory syndrome (SARS) [ref 1](#)  
severe combined immunodeficiency [ref 1](#)  
sex hormone binding globulin [ref 1](#)  
sex steroids [ref 1](#)  
sexual abuse [ref 1](#), [ref 2](#)  
Shipman, Harold [ref 1](#)  
shock [ref 1](#)  
short stature [ref 1](#)  
    assessment [ref 1](#)  
    causes [ref 1](#)  
    constitutional [ref 1](#)  
    familial [ref 1](#)  
    investigation [ref 1](#)  
short-bowel syndrome [ref 1](#)  
short-rib polydactyly syndromes [ref 1](#)  
shunt nephritis [ref 1](#)  
shunt operation [ref 1](#)  
shunts  
    left to right [ref 1](#)  
    mixed [ref 1](#)  
    right to left [ref 1](#)  
sick sinus syndrome [ref 1](#)  
sick thyroid syndrome [ref 1](#)  
sickle cell retinopathy [ref 1](#)  
sickle-cell disease [ref 1](#)  
sickle-cell trait [ref 1](#)  
sickle-cell-Hb C disease [ref 1](#)  
SIDS *see* sudden infant death syndrome  
significance tests [ref 1](#)  
sildenafil [ref 1](#)  
Silver-Russell syndrome [ref 1](#)  
sinusitis [ref 1](#)  
Sipple syndrome [ref 1](#)  
situs [ref 1](#), [ref 2](#)  
Sjögren syndrome [ref 1](#)  
Sjögren-Larsson syndrome [ref 1](#)  
skeletal survey [ref 1](#)  
skewed distributions [ref 1](#)  
skin  
    biopsy [ref 1](#)  
    embryology [ref 1](#)

neonatal skin disorders [ref 1](#)  
structure and function [ref 1](#)  
skull fractures [ref 1](#)  
slapped cheek syndrome *see* parvovirus B19  
sleep disordered breathing [ref 1](#)  
sleep disorders [ref 1](#)  
sleep problems [ref 1](#)  
sleep stages [ref 1](#)  
sleepwalking [ref 1](#)  
slipped capital femoral epiphysis [ref 1](#)  
slit-lamp biomicroscopy [ref 1](#)  
small intestine [ref 1](#)  
small-for-gestational-age babies [ref 1](#)  
Smith-Lemli-Opitz syndrome [ref 1](#), [ref 2](#)  
smoking, and SIDS [ref 1](#)  
smoking, effects on fetus and newborn [ref 1](#)  
snake bites [ref 1](#)  
social skills [ref 1](#)  
sodium valproate [ref 1](#)  
somatic hypermutation [ref 1](#)  
somatic recombination [ref 1](#)  
sorbitol [ref 1](#)  
Sotos syndrome [ref 1](#)  
spasmus nutans [ref 1](#)  
special education needs [ref 1](#), [ref 2](#)  
speech discrimination test [ref 1](#)  
speech and language [ref 1](#)  
    clinical assessment [ref 1](#)  
    delay [ref 1](#)  
    diagnosis of problems [ref 1](#)  
sphingolipidoses [ref 1](#), [ref 2](#)  
    Fabry disease [ref 1](#), [ref 2](#)  
    Gaucher disease [ref 1](#), [ref 2](#)  
    Niemann-Pick disease [ref 1](#), [ref 2](#)  
    Tay-Sachs disease [ref 1](#), [ref 2](#)  
spina bifida [ref 1](#), [ref 2](#), [ref 3](#)  
spinal muscular atrophy [ref 1](#), [ref 2](#)  
spinal shock [ref 1](#)  
Spitz naevus [ref 1](#)  
squint [ref 1](#), [ref 2](#)  
stabbing [ref 1](#)  
standard deviation [ref 1](#), [ref 2](#)  
standard error [ref 1](#)  
staphylococcal scalded skin syndrome [ref 1](#)  
statementing [ref 1](#)

statistical power [ref 1](#)  
statistics [ref 1](#)  
    confidence intervals [ref 1](#)  
    correlation and regression [ref 1](#)  
    distributions [ref 1](#)  
    inappropriate summaries for numeric data [ref 1](#)  
    missing data [ref 1](#)  
    multiple testing without adjustment [ref 1](#)  
    non-independent measurements treated as independent [ref 1](#)  
    patients acting as their own controls [ref 1](#)  
    screening tests [ref 1](#)  
    significance tests [ref 1](#)  
    study design [ref 1](#)  
    testing group changes independently [ref 1](#)  
status epilepticus [ref 1](#)  
stavudine [ref 1](#)  
sternal clefts [ref 1](#)  
steroid creams [ref 1](#)  
steroid sulphatase deficiency [ref 1](#)  
Stevens-Johnson syndrome [ref 1](#)  
stillbirth [ref 1](#)  
Still's murmur [ref 1](#)  
stings [ref 1](#)  
stomach [ref 1](#)  
storage disorders [ref 1](#)  
strawberry naevi [ref 1](#)  
strawberry tongue [ref 1](#)  
streptokinase [ref 1](#)  
stridor [ref 1](#)  
study design [ref 1](#)  
Sturge-Weber syndrome [ref 1](#), [ref 2](#), [ref 3](#)  
subacute sclerosing panencephalitis [ref 1](#), [ref 2](#)  
subconjunctival haemorrhage [ref 1](#)  
subdural haematoma [ref 1](#)  
subglottic stenosis [ref 1](#)  
sucrase-isomaltase deficiency [ref 1](#)  
sudden infant death syndrome [ref 1](#)  
    communication checklist [ref 1](#)  
    definition [ref 1](#)  
    follow-up [ref 1](#)  
    incidence [ref 1](#)  
    physical examination [ref 1](#)  
    protective factors [ref 1](#)  
    risk factors [ref 1](#)  
    sample taking [ref 1](#)



- support for family [ref 1](#)
- suicidal behaviour [ref 1](#)
- suicide [ref 1](#)
- Supervision Order [ref 1](#)
- supratentorial tumours [ref 1](#)
- supraumbilical hernia [ref 1](#)
- supraventricular tachycardia [ref 1](#), [ref 2](#), [ref 3](#)
- surface area [ref 1](#)
- surfactant deficiency [ref 1](#)
- surgery [ref 1](#)
  - general paediatric [ref 1](#)
  - neonatal [ref 1](#)
- suxamethonium sensitivity [ref 1](#)
- swine flu [ref 1](#)
- switch operation [ref 1](#)
- Sydenham's chorea [ref 1](#)
- syncope [ref 1](#)
- syndrome of inappropriate antidiuretic hormone secretion [ref 1](#)
- syphilis [ref 1](#)
- syphilis, congenital [ref 1](#), [ref 2](#)
- systemic inflammatory response syndrome [ref 1](#)
- systemic lupus erythematosus [ref 1](#)
  - drug-induced [ref 1](#), [ref 2](#)
  - and fetal malformations [ref 1](#)
  - maternal, effects on fetus and newborn [ref 1](#)
  - nephritis [ref 1](#)

- T-cell receptor excision circles (TRECs) [ref 1](#)
- T-cells [ref 1](#), [ref 2](#)
- T-helper cells [ref 1](#)
- T-regulatory cells [ref 1](#)
- t*-test [ref 1](#)
- tachycardia [ref 1](#), [ref 2](#)
  - causes [ref 1](#)
  - supraventricular [ref 1](#), [ref 2](#), [ref 3](#)
  - ventricular [ref 1](#), [ref 2](#), [ref 3](#)
- tacrolimus [ref 1](#), [ref 2](#)
- Takayasu disease [ref 1](#)
- talipes equinovarus [ref 1](#)
- tall stature [ref 1](#)
  - assessment [ref 1](#)
  - causes [ref 1](#)
  - constitutional obesity [ref 1](#)
  - familial [ref 1](#)
  - investigation [ref 1](#)

Tanner stages of puberty [ref 1](#)  
Tay-Sachs disease [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#)  
Tay's syndrome [ref 1](#)  
teeth [ref 1](#)  
telecanthus [ref 1](#)  
telogen effluvium [ref 1](#)  
temper tantrums [ref 1](#)  
teratogens [ref 1](#), [ref 2](#)  
teratoma [ref 1](#)  
    sacrococcygeal [ref 1](#)  
testes, impalpable [ref 1](#)  
testicular torsion [ref 1](#)  
tetanus vaccine [ref 1](#), [ref 2](#)  
tetralogy of Fallot [ref 1](#), [ref 2](#)  
thalassaemia [ref 1](#)  
thanatophoric dysplasia [ref 1](#)  
theophylline, half-life [ref 1](#)  
thiopentone coma [ref 1](#)  
Thomsen disease [ref 1](#)  
thoracic surgery [ref 1](#)  
throat [ref 1](#)  
thrombocytopenia [ref 1](#)  
    alloimmune neonatal [ref 1](#)  
    drug-induced [ref 1](#)  
    human immunodeficiency virus [ref 1](#)  
    maternal, effects on fetus and newborn [ref 1](#)  
    neonatal isoimmune [ref 1](#)  
thrombocytopenia and absent radius syndrome [ref 1](#)  
thyroglossal cyst [ref 1](#)  
thyroid gland [ref 1](#)  
    anatomy [ref 1](#)  
    disorders  
        hyperthyroidism [ref 1](#)  
        hypothyroidism [ref 1](#)  
        maternal, effects on fetus and newborn [ref 1](#)  
        neoplasia [ref 1](#)  
    physiology [ref 1](#)  
thyroid-stimulating hormone [ref 1](#)  
tiagabine [ref 1](#)  
tics [ref 1](#), [ref 2](#)  
tinea [ref 1](#)  
tinea capitis [ref 1](#)  
tinea corporis [ref 1](#)  
tinea cruris [ref 1](#)  
tinea pedis [ref 1](#)

tinea versicolor [ref 1](#)  
tissue plasminogen activator [ref 1](#)  
toddler's diarrhoea [ref 1](#)  
toe walking [ref 1](#)  
tonsillitis [ref 1](#)  
topiramate [ref 1](#)  
torticollis [ref 1](#)  
total anomalous pulmonary venous connection [ref 1](#)  
total body water [ref 1](#), [ref 2](#)  
total parenteral nutrition [ref 1](#), [ref 2](#)  
    complications [ref 1](#)  
    home [ref 1](#)  
    indications for [ref 1](#)  
    monitoring [ref 1](#)  
    prescribing [ref 1](#)  
Tourette's syndrome [ref 1](#)  
toxic epidermal necrolysis [ref 1](#)  
toxic shock syndrome [ref 1](#)  
toxicology [ref 1](#)  
    aspirin overdose [ref 1](#)  
    button batteries [ref 1](#)  
    carbon monoxide [ref 1](#)  
    iron [ref 1](#)  
    lead poisoning [ref 1](#)  
    paracetamol [ref 1](#)  
    tricyclic antidepressants [ref 1](#)  
toxocariasis [ref 1](#)  
toxoplasmosis [ref 1](#), [ref 2](#)  
    congenital [ref 1](#), [ref 2](#)  
    and fetal malformations [ref 1](#)  
tracheitis [ref 1](#)  
tracheo-oesophageal fistula [ref 1](#), [ref 2](#), [ref 3](#)  
tracheomalacia [ref 1](#)  
transient hypogammaglobulinaemia of infancy [ref 1](#)  
transient neonatal pustulosis melanosis [ref 1](#)  
translocations [ref 1](#)  
transposition of great arteries [ref 1](#), [ref 2](#)  
trauma [ref 1](#), [ref 2](#)  
    and breathing difficulties [ref 1](#)  
travellers' diarrhoea [ref 1](#)  
tricarboxylic acid cycle [ref 1](#)  
trichothiodystrophy [ref 1](#), [ref 2](#)  
trichotillomania [ref 1](#)  
tricuspid atresia [ref 1](#)  
tricyclic antidepressants, poisoning [ref 1](#)

trigger thumb [ref 1](#)  
trinucleotide repeat disorders [ref 1](#)  
triple X syndrome [ref 1](#)  
triploid [ref 1](#)  
trisomy [ref 1](#), [ref 2](#)  
tropical diseases [ref 1](#)  
truancy [ref 1](#)  
tuberculin tests [ref 1](#)  
tuberculosis [ref 1](#), [ref 2](#)  
    congenital [ref 1](#)  
    diagnosis [ref 1](#)  
    neonatal contact for mothers [ref 1](#)  
    symptoms and signs [ref 1](#)  
    treatment [ref 1](#)  
tuberous sclerosis [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#), [ref 5](#), [ref 6](#)  
tumour-lysis syndrome [ref 1](#)  
Turner syndrome [ref 1](#), [ref 2](#)  
Turner's syndrome [ref 1](#)  
twenty nail dystrophy [ref 1](#)  
tympanometry [ref 1](#)  
type I errors [ref 1](#)  
type II errors [ref 1](#)  
typhoid [ref 1](#)  
tyrosinaemia [ref 1](#)  
tyrosine kinase receptors [ref 1](#)

ulcerative colitis [ref 1](#)  
ultrasonography  
    ocular [ref 1](#)  
    renal [ref 1](#)  
umbilical hernia [ref 1](#)  
UN Convention of Rights of the Child [ref 1](#)  
unbalanced translocations [ref 1](#)  
undescended testis [ref 1](#)  
upper airway obstruction [ref 1](#)  
    intentional [ref 1](#)  
urate [ref 1](#)  
urea cycle defects [ref 1](#), [ref 2](#)  
ureterocele [ref 1](#)  
urinalysis [ref 1](#)  
urinary tract  
    congenital abnormalities [ref 1](#)  
    infection [ref 1](#)  
urine microscopy [ref 1](#)  
urological abnormalities [ref 1](#)

urticaria [ref 1](#)  
urticaria pigmentosa [ref 1](#)  
utilitarianism [ref 1](#)  
uveal tract disorders [ref 1](#)  
uveitis [ref 1](#)  
    anterior [ref 1](#)  
    posterior [ref 1](#)

vaccination  
    Bacillus Calmette-Guérin (BCG) vaccine [ref 1](#), [ref 2](#), [ref 3](#)  
    diphtheria [ref 1](#)  
    *Haemophilus influenzae* type B vaccine [ref 1](#), [ref 2](#)  
    hepatitis B [ref 1](#), [ref 2](#)  
    immunosuppressed patients [ref 1](#)  
    live vaccines [ref 1](#)  
    meningitis C [ref 1](#), [ref 2](#)  
    MMR [ref 1](#), [ref 2](#)  
    pertussis [ref 1](#), [ref 2](#)  
    polio [ref 1](#), [ref 2](#)  
    rubella [ref 1](#), [ref 2](#)  
    tetanus [ref 1](#), [ref 2](#)

vaccinations, reactions to [ref 1](#)  
VACTERL [ref 1](#)  
varicella, congenital [ref 1](#)  
varicella zoster virus [ref 1](#)  
vascular malformations [ref 1](#)  
vascular rings [ref 1](#)  
vascular slings [ref 1](#)  
vasoactive intestinal peptide [ref 1](#)  
VATER (VACTERL) association [ref 1](#)  
venous hum [ref 1](#)  
venous thrombosis [ref 1](#)  
ventilation [ref 1](#)  
ventilatory support [ref 1](#)  
ventricular fibrillation [ref 1](#)  
ventricular septal defect [ref 1](#), [ref 2](#)  
ventricular tachycardia [ref 1](#), [ref 2](#), [ref 3](#)  
ventriculoarterial connection [ref 1](#)  
vernal conjunctivitis [ref 1](#)  
very low-density lipoprotein [ref 1](#)  
vigabatrin [ref 1](#)  
viral conjunctivitis [ref 1](#)  
viral haemorrhagic fevers [ref 1](#)  
viral infections [ref 1](#)  
virtue ethics [ref 1](#)

vision [ref 1](#)  
visual acuity [ref 1](#)  
visual evoked potentials [ref 1](#)  
visual fields [ref 1](#)  
visual impairment [ref 1](#)  
visual loss, acquired [ref 1](#)  
vitamin A [ref 1](#)  
vitamin B<sub>12</sub> [ref 1](#)  
vitamin D [ref 1](#), [ref 2](#)  
    metabolism [ref 1](#)  
vitamin E [ref 1](#)  
vitamin K [ref 1](#)  
    deficiency [ref 1](#), [ref 2](#)  
vitiligo [ref 1](#)  
volume of distribution [ref 1](#)  
von Gierke disease [ref 1](#)  
von Hippel-Lindau disease [ref 1](#), [ref 2](#)  
von Recklinghausen's disease [ref 1](#)  
von Willebrand disease [ref 1](#), [ref 2](#)

wardship [ref 1](#), [ref 2](#)  
warfarin [ref 1](#)  
warts [ref 1](#)  
    perianal [ref 1](#)  
water regulation [ref 1](#)  
watering eye [ref 1](#)  
Wegener granulomatosis [ref 1](#)  
weight [ref 1](#)  
Wermer syndrome [ref 1](#)  
West Nile virus [ref 1](#)  
wet wraps [ref 1](#)  
white cells  
    lymphocytes [ref 1](#)  
    phagocytes [ref 1](#)  
Williams syndrome [ref 1](#), [ref 2](#)  
Wilms' tumour [ref 1](#)  
Wilson disease [ref 1](#), [ref 2](#), [ref 3](#), [ref 4](#), [ref 5](#)  
Wiskott-Aldrich syndrome [ref 1](#), [ref 2](#)  
Wolff-Hirschhorn syndrome [ref 1](#)

X-linked adrenoleukodystrophy [ref 1](#), [ref 2](#)  
X-linked agammaglobulinemia [ref 1](#), [ref 2](#), [ref 3](#)  
X-linked chronic granulomatous disease [ref 1](#)  
X-linked dominant conditions [ref 1](#)  
X-linked hyper-IgM syndrome [ref 1](#)

X-linked hypophosphataemic rickets [ref 1](#)

X-linked lymphoproliferative disease [ref 1](#)

X-linked recessive conditions [ref 1](#)

X-linked recessive ichthyosis [ref 1](#)

xeroderma pigmentosum [ref 1](#)

47,XYY males [ref 1](#)

Zellweger syndrome [ref 1](#), [ref 2](#), [ref 3](#)

zidovudine [ref 1](#)

zinc [ref 1](#)

abnormalities [ref 1](#)

Zollinger-Ellison syndrome [ref 1](#)

## ENDNOTES

1. Where two or more injections are required at once, these should ideally be given in different limbs. Where this is not possible, injections in the same limb should be given 2.5 cm apart.
2. Please refer to notes above for general contraindications to immunizations.
3. All immunizations may be complicated by local or general side effects as discussed above. DTP, diphtheria + tetanus + pertussis; DT, diphtheria + tetanus; OPV, oral polio vaccine; Hib, *Haemophilus influenzae* type b; MMR, measles, mumps, rubella; CSM, Committee on Safety of Medicines (now the Commission on Human Medicines, incorporating the CSM and the Medicines and Healthcare products Regulatory Agency); Men C, meningitis C.
4. **The ‘Back to Sleep’ Campaign**, whereby parents are educated re the protective effect of supine infant sleeping, is well documented to have led to a very significant drop in the incidence of SIDS in the UK over the last two decades. Similar campaigns have also been successful in other countries such as New Zealand, Scandinavia and the USA.
5. **Smoking** increases the risk of SIDS by up to threefold. There is an increase in risk with increased likelihood of spontaneous apnoea and decreased ability to compensate after such an episode. Such effects are likely to be enhanced by intercurrent illness.
6. Do not confuse with glucose-6-phosphate dehydrogenase deficiency (favism) which is X-linked recessive.  
Most metabolic disorders are autosomal recessive – remember the exceptions.
7. Conditions that can also present as acute liver failure
8. The ‘e’ antigen is absent in pre-core mutant.
9. If abnormal consider MCUG (micturating cystourethrogram).
10. Although MCUG should not be performed routinely it should be considered if the following features are present: dilatation on ultrasonography, poor urine flow, non-*E. coli*-infection, family history of vesicoureteric reflux.
11. Ultrasonography in toilet-trained children should include assessment of post-micturition bladder volume, as a guide to bladder emptying.





# PasTest®

---

Dedicated to your success

**What did you think of this book?**

# Click here to let us know!

**pastest.co.uk**



**twitter.com/PasTest**



**joinourgroup**